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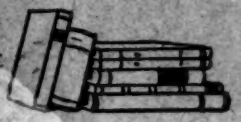

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 2 1953

COMBINED CHEMOTHERAPY IN BACTERIAL INFECTIONS*

BY

L. P. GARROD, M.D., F.R.C.P.

Bacteriologist, St. Bartholomew's Hospital; Professor of Bacteriology in the University of London

The practice of combining two or even more chemotherapeutic drugs in the treatment of patients is growing commoner, and its merits demand examination. Inquiry soon reveals that the subject is one of great complexity, and that for various reasons these combinations may often be useful, sometimes may be no better than one of the pair used alone, and at least occasionally may be contraindicated because a diminished instead of an enhanced effect results. The laboratory work sometimes required for the intelligent direction of such treatment is perhaps more elaborate and time-consuming than anything previously undertaken in routine clinical bacteriology.

Some Indications for Combined Therapy

The Urgent Undiagnosed Case.—An acutely ill patient evidently suffering from some infection, in whom no bacteriological (and perhaps even no clinical) diagnosis has been made, may require treatment with one antibiotic or another, and it is perhaps tempting to give him both until the situation is clarified. This is often done, but genuine necessity for it should be very exceptional. Premature and blindly directed treatment may obscure the diagnosis, and should not be begun until any specimens have been obtained the examination of which is likely to be helpful.

Mixed and Double Infections.—There are some infections, notably those originating in the bowel, but also including some involving the lungs, the flora of which is so varied that no single drug may be expected to combat the whole of it. In peritonitis due to perforation of the lower part of the bowel treatment with both penicillin and streptomycin has been common practice and is theoretically sound, although I know of no statistical proof of its efficacy. It may well be superseded by the use of the newer antibiotics with their wider range of activity: terramycin, given at first intravenously, has in my experience been particularly effective.

A patient may, on the other hand, have two separate conditions, due to entirely different bacteria: perhaps the commonest of such pairs is a lung infection complicating one of the urinary tract or vice versa. If it should be thought necessary to treat both together no single drug may serve for both, and two may therefore be needed.

Prevention of Toxic Effects.—Another possible indication for using two drugs is the danger of toxic effects from only one. In this category comes the use of sulphonamide combinations—for example, "sulphatriad"—an advantage of which is that each component retains its individual solubility in the urine, with the result that the risk of heavy crystalline deposition and consequent tubular or ureteric blockage is minimized. Among antibiotics, streptomycin is that most liable to produce toxic effects, and any effective combination with it which enabled the dose of streptomycin to be reduced from a risky to a safe level might have this type of advantage.

These three indications are of much less significance than the prevention of acquired resistance and the achievement of synergism.

Prevention of Acquired Resistance

Acquired bacterial resistance is a change which threatens ultimately to extinguish the usefulness of all the present major antibiotics except penicillin. Its gradual development in communities where these drugs are freely available can be delayed in only two ways. One is more discriminating and restricted use, and, to judge by experience hitherto, much cannot be hoped from this direction. The second is to combine with the main drug another with an adjuvant effect. The other may not only exert its own independent effect but prevent acquisition of resistance to the first. Precisely how this is achieved we cannot pretend to say until more is known of the mode of action of antibiotics, but in general terms the mechanism is almost certainly this. Sulphonamides act by blocking a stage in an essential synthesis, and antibiotics probably act similarly. The acquisition of resistance results from a circumvention of this chemical process, another being substituted for it having the same ultimate effect, with which the antibiotic cannot interfere. If the second drug used blocks this second process the alternative metabolic route cannot be established, and the organism therefore remains sensitive.

If this explanation is true, it is perhaps remarkable that so many combinations do act in this way, and it encourages the belief that by this means itself more may be discovered about the points of attack of individual drugs. In practice it may even prove advantageous to use more than two drugs together: Carpenter *et al.* (1945) found that gonococci could be entirely prevented from acquiring resistance to sulphathiazole, rivanol, promanide, and penicillin only by exposing them to all four together, a combination of the first three not being fully effective. Similar *in vitro* studies with antibiotics have been made by Kaipainen (1951, 1952), who has shown that a mutual resistance-preventing relationship exists between streptomycin on the one hand and aureomycin, chloramphenicol, or terramycin on the other. (It does not follow that

*Based on a Holme Lecture delivered at University College Hospital on February 12, 1953.

these actual combinations will be therapeutically effective, and indeed there is at least a theoretical objection to them on other grounds.) Streptomycin, as the antibiotic to which high resistance is most readily acquired, stands most in need of a partner to prevent this, particularly when it has to be given for long periods, as in the treatment of tuberculosis. Its combination with *p*-aminosalicylic acid, now regarded as obligatory for the treatment of this disease, has been clearly shown to have this effect, provided that the dose of P.A.S. is adequate (Report, 1949 ; Daniels and Hill, 1952), as well as securing an improved therapeutic response. The combination of streptomycin with isoniazid also militates against the acquisition of resistance to either (Report, 1953).

Synergism

Another notable advantage of combined therapy can be (but by no means always is) the achievement of a synergic effect. This is one of three possible results of combining two drugs, and the terms describing them require definition. In the simplest terms, an additive effect is the sum of those of the same dose of each drug given separately ; a synergic effect is something more than this, and an antagonistic effect something less. If these effects can be observed in the form of clinical therapeutic results they are undeniable : if, on the other hand, we are referring to something capable of assessment in the laboratory the definition must be extended by an explanation of what effect is meant. The most easily observed effect is simple inhibition of visible growth, and it is not surprising that so many workers have studied both single and combined effects by this standard only. Unfortunately it is inadequate and misleading for certain combined effects, and a true picture of them can be obtained only by studying bactericidal instead of merely bacteriostatic action, and preferably by following its progress in a series of observations. The definition of synergism proposed by Jawetz and Gunnison (1952a), whose studies of combined drug effects have contributed so largely to our present knowledge, is : " A large increase in the rate of early bactericidal action and the rate of cure of infections beyond that obtainable by simple additive effects of the agents."

An ultimately fatal case of *Str. faecalis* endocarditis was the incentive for Jawetz's (1952) work, and it is in this disease that we find the clearest example of antibiotic synergism yet known. Jawetz and his colleagues showed that when *Str. faecalis* is exposed to an optimal concentration of penicillin the initial bactericidal effect is incomplete and is followed eventually by growth ; if, on the other hand, streptomycin is added, even in a concentration quite ineffective acting alone, the initial rate of killing is accelerated and continues to the point of total sterilization (Jawetz and Gunnison, 1950). That this combination of drugs offers the only hope of cure in this infection is now fairly well recognized, and is evident from the extensive series of cases described by Robbins and Tompsett (1951). We have treated four cases of this infection at St. Bartholomew's Hospital : three were included in the four cases of penicillin-resistant bacterial endocarditis reported by Cates, Christie, and Garrod (1951), and the fourth is more recent. The antibiotic sensitivities of the organisms from these patients, stated in the Table, are strikingly uniform, and would seem to demand some other treatment than that which in fact was required. All four strains were highly sensitive to aureomycin, yet a six-weeks course of this drug was ineffective in Case 1, and an eight-weeks course, during the latter half of which the dose was 8 g. daily, was equally so in Case 2. Case 3 had a 10-weeks course of chloramphenicol, and Case 4 shorter courses of several drugs without effect (most of all this treatment was given elsewhere). The infection was controlled in all four patients by penicillin and streptomycin, although two of the patients died from heart failure, Case 1 after and Case 3 during treatment.

Antibiotic Sensitivities of Four Strains of Str. faecalis Isolated from Cases of Endocarditis; St. Bartholomew's Hospital, 1950–2

Sex	Age	Inhibitory Concentrations (μg./ml.)			
		Penicillin	Streptomycin	Aureomycin	Chloramphenicol
F	36	2·5	30	0·15	20
M	57	1·8	30	0·1	6
M	63	2·5	125	0·15	2·5
F	25	2·5	10	0·3	0·6

In relation to the task which chemotherapy has to perform, bacterial endocarditis is certainly an exceptional disease and possibly unique. It is not enough, as in most other infections, to prevent further bacterial growth and leave the disposal of survivors to the body defences ; this is a disease in which those defences are powerless. It is probably true to say that chemotherapy must eliminate the last surviving streptococcus in the vegetations if relapse is not to occur. That a bactericidal drug (penicillin) should be necessary, or in this particular infection a highly bactericidal combination, is not surprising. There are few reports of cures of this disease by any of the newer antibiotics.

In treating *Str. faecalis* endocarditis we have hitherto assumed that the higher the concentration of each drug that can be maintained in the blood the better, and our patients have accordingly been given large doses of both. The two survivors in the earlier series (Cates, Christie, and Garrod, 1951) both suffered severe vestibular damage from having received 4 g. of streptomycin daily for six and seven weeks, and in our recent case the dose was limited to 2 g. daily in the hope of obviating this effect. There is another possible reason for limiting the dose not of streptomycin but of penicillin. It has been shown by Eagle and Musselman (1948) that *Str. faecalis* is one of the species subject to the zone phenomenon in the bactericidal action of penicillin : the optimum concentration is about 6 μg. (10 units) per ml., and concentrations higher than this kill the organism more slowly. Whether this paradoxical effect operates when streptomycin is also present is of some interest: according to Gunnison, Jawetz, and Coleman (1950) it does not. Strains of *Str. faecalis* from two of our cases were tested to verify this. Both exhibited the zone phenomenon when exposed to penicillin only, a concentration of 10 μg. per ml. killing more rapidly than 500 μg. per ml. When 10 or 20 μg. per ml. of streptomycin was combined with these and intermediate concentrations of penicillin, the much accelerated death rate varied little with the latter, the higher concentrations sometimes giving a slightly faster kill and sometimes not. It appears from these results that little is either gained or lost by massive penicillin dosage in this combination, but there is some suggestion in results obtained by Martin, Chabbert, and Sureau (1953, Table I) by a rather different method that intermediate concentrations are the most effective.

Str. faecalis endocarditis is an exceptional disease, and it may well be asked whether the drug combination required for its treatment is indicated in any other condition. It may be indicated in other exceptional cases which can be identified as requiring it only by elaborate *in vitro* tests: the need for it in mixed infections such as peritonitis has to a large extent been removed by the advent of the new " broad spectrum " antibiotics. The indiscriminate use of penicillin-streptomycin combinations is certainly to be deplored, and it may be thought unfortunate that proprietary mixtures of these two antibiotics, having flourished on the American market for some time, have now been introduced in this country. That these are commercially successful is due to two ideas about them—that they are generally more potent than penicillin itself, and that they afford wider cover in the undiagnosed case. The logical outcome of the latter standpoint would be a chemotherapeutic cocktail supposedly capable of dealing with any microbic infection, and given automatically to any patient with fever. Apart from the general

undesirability of "shot-gun" therapy, the use of streptomycin in patients of whom at least nine-tenths will probably get no benefit from it is to be deprecated on three grounds—the possibility of either toxic effects or sensitization, and the likelihood of evoking bacterial resistance. These and other weighty reasons for discouraging the use of these combinations have been formulated by Jawetz and Gunnison (1952b) in a report published by the Council on Pharmacy and Chemistry of the American Medical Association.

Laboratory Tests of Combined Action

Repeated viable counts in various mixtures and the plotting of death curves constitute a major operation in any laboratory and are almost beyond the capacity of some. A simpler method of determining combined effects must consequently be found if laboratory guidance for such treatment is to be provided. Unfortunately, simple tests of growth inhibition, at least by pairs of antibiotics, seem to be worthless. A few examples from many studies made in this way will show how misleading their results can be. Richter (1952), in a long series of such tests, found that there was not even an additive effect between streptomycin and penicillin acting on *Str. faecalis*, although this is perhaps the clearest example of a synergic combination that we know. Reid, Jones, and Bryce (1952) found that most combinations of five antibiotics acting on four species of Gram-negative bacilli gave an enhanced effect, although one of their combinations, penicillin+chloramphenicol, has been proved by more appropriate methods, including therapeutic tests, to be antagonistic. In some experiments by Bigger (1950) P.A.S. and streptomycin were made under certain conditions to appear antagonistic. Price, Randall, Welch, and Chandler (1949) tested various combinations not only in this way but therapeutically in mice, and obtained agreement between the two methods in only 50% of their results, some being frankly contradictory.

These authors used liquid media; others have hoped to demonstrate synergism even more simply by an agar diffusion method. That this hope is vain may be concluded from the findings of Peyré and Velu (1952), who tested combinations both in plates and in agar columns in tubes, and found that the width or depth of the inhibition zone differed little from that given by the more rapidly diffusing and active of the pair acting alone. It has also been suggested, and found impracticable, to determine combined effect in a plate in which two antibiotics diffuse from paper strips or gutters meeting at a right angle. I have been unable to obtain true or even consistent results in trials of this method. The fact undoubtedly is that mere inhibition of growth, as judged by naked-eye appearance, affords no true reflection of what a combination of drugs does to bacteria. What matters therapeutically is whether the combination kills them, and in a culture showing no visible growth the bacteria may either have been killed within an hour or may even be slowly multiplying.

There is thus no alternative to a method involving the enumeration of survivors after a period of exposure to the drugs. That proposed by Martin, Sureau, and Chabbert (1952) is not unduly complex, and in their hands has afforded a guide to successful treatment. If four antibiotics—for example, penicillin, streptomycin, chloramphenicol, and terramycin—are to be tested singly and in every possible combination, only ten tubes of broth are required, provided that only a single concentration of each antibiotic is to be tested. After incubation for 24 hours or less a measured inoculum from each is spread over a segment of a plate: decimal dilutions of the culture used for inoculation are plated similarly, only four plates being required in all. By comparison with this control it can be seen whether the inoculum in the tubes has multiplied or diminished in numbers: if the latter, the result can be stated as a very approximate percentage surviving.

The difficulty with such a simplified method is to choose appropriate single concentrations of the antibiotics, since to vary them would immediately complicate it: even two concentrations instead of one would mean 36 tubes instead of 10. They can evidently be chosen on either of two principles: in relation to the sensitivity of the organism to each used singly or in relation to the concentrations attained in the body by the dosage it is proposed to use. Arbitrary amounts chosen on the latter basis are preferable for routine use. The test is certainly worthy of extended trial as a guide to treatment in difficult cases.

We have recently applied a simple three-tube form of this test to determining whether the penicillin–streptomycin synergy against *Str. faecalis* which can be demonstrated by this as well as by more elaborate methods is also exerted against other species. Some strains of *Bact. coli*, *Proteus*, and penicillin-resistant *Staph. pyogenes* reacted similarly, suggesting that this combination may have uses other than the treatment of bacterial endocarditis.

Sulphonamide–Antibiotic Combinations

I was responsible eight years ago (Garrod, 1945) for a misleading although correct observation—namely, that, as observed by viable counts over an eight-hour period, sulphathiazole reduces the rate at which penicillin kills staphylococci. An explanation of this was not far to seek: penicillin is active only against multiplying bacteria, and another agent which prevents multiplication therefore removes a condition necessary for at least its full effect. The defect of this experiment was that it was terminated too early. Others who have prolonged such experiments have shown that the initial rapid decline produced by penicillin alone may be succeeded by bacterial recovery and actual growth, whereas the slower decline caused by penicillin and a sulphonamide continues and proceeds to ultimate extinction. The explanation for this suggested by Hobby and Dawson (1946) and by Klein and Kalter (1946) is that penicillin reduces the number of living bacteria to a level at which a sulphonamide can exert its full effect: the dependence of sulphonamide activity on bacterial numbers is well known. This is therefore not so much synergy in the ordinary sense as two successive and complementary effects. It is evident from the work of the authors quoted that the result is conditioned by various factors, and, among these, time relationships between the introduction of the two drugs have been particularly studied by Gunnison, Speck, Jawetz, and Bruff (1951), who draw an interesting distinction between the apparent interfering effects of sulphonamides and the newer antibiotics with the bactericidal action of penicillin.

Simple tests of growth inhibition have consistently shown that an enhanced effect is obtained by combining penicillin and a sulphonamide: in this connexion Bigger's (1946) work on *Salm. typhi* may be recalled; Thomas and Hayes (1947) and Stewart (1947) obtained similar results with the same organism, and Bigger (1944) previously showed that they were obtainable with *Staph. pyogenes*. Most authors who have tested penicillin–sulphonamide combinations therapeutically in mice (Ungar, 1943; Soo-Hoo and Schnitzer, 1944; Nitti, Boyer, and Faguet, 1946; Kolmer, 1948; Domagk, 1952) have observed synergic effects. There have been fewer studies of the combined action of sulphonamides and streptomycin, but Klein and Kimmelman (1947) and Knapp (1950) report mutual reinforcement by such combinations, and the former emphasize particularly that the presence of a sulphonamide tends to prevent the development of bacterial resistance to streptomycin.

Clinical experience confirms the general tenor of these findings in two particulars. Waring and Smith (1944) are emphatic that sulphadiazine must be given in addition to penicillin for the treatment of pneumococcal meningitis; 11 out of 12 patients so treated recovered, whereas penicillin alone was less successful. Smith, Duthie, and Cairns (1946) base the same conclusion on a study of 38 cases. The second clear example is provided by the action of streptomycin and sulphadiazine in brucellosis, which was the only effective treatment for this disease until the discovery of aureomycin and chloramphenicol (Spink, Hall, Shaffer, and Braude, 1948; Scowen and Garrod, 1948).

Antagonistic Effects

Although interference by sulphonamides with the action of penicillin is only apparent, interference by other antibiotics due to a similar mechanism is not merely demonstrable in a similar way *in vitro*, but verifiable by therapeutic tests. That aureomycin may interfere with the action of penicillin or streptomycin was first shown by Lankford and Lacy (1949), but most of our now extensive knowledge of this subject is due to the work of Jawetz and his colleagues, which has been summarized in recent reviews (Jawetz, 1952; Jawetz and Gunnison, 1953). The stages in the development of this work were as follows. It was first shown that chloramphenicol interferes with the bactericidal action of penicillin *in vitro* (Jawetz, Gunnison, and Coleman, 1950), and later that aureomycin and terramycin have a similar interfering effect (Gunnison, Coleman, and Jawetz, 1950). The interfering action of chloramphenicol had meanwhile been confirmed therapeutically (Jawetz and Speck, 1950): mice infected with *Str. pyogenes* and treated with both chloramphenicol and penicillin had a lower survival rate than those treated with the same dose of either drug alone. The objection that such acute experiments, in which only a single dose of the drug or drugs is given, are far removed from the conditions of clinical use appears to be answered by later studies (Speck and Jawetz, 1952) of a subacute streptococcal infection produced by intramuscular inoculation, of which control mice died in five to eight days. Although treatment was continued for five days, the same type of effect was observed, chloramphenicol and particularly terramycin reducing survivors to as low as 45% when combined with a dose of penicillin which alone saved 100%. In another series of experiments, both *in vitro* and *in vivo*, it was shown that the newer antibiotics also interfere with the action of streptomycin, chloramphenicol having the most pronounced effect (Jawetz, Gunnison, and Speck, 1951a).

The explanation of these findings is as follows (Jawetz and Gunnison, 1952a). Antibiotics are divisible into two classes:—Group 1 (bactericidal): penicillin, streptomycin, bacitracin, neomycin. Group 2 (bacteriostatic): aureomycin, chloramphenicol, terramycin.

Combinations within group 1 are often synergic. Within group 2 they are no more than additive. Combinations of the two groups are apt to be antagonistic, the group 2 drug interfering with the bactericidal action of the other. Such antagonism is observed only when the organism is fully sensitive to the bactericidal component: if it is more resistant (although naturally not if completely so) the combination may actually be synergic. Instances of this paradoxical effect are cited by Jawetz, Gunnison, and Speck (1951b), and by Spies *et al.* (1951); both patients had staphylococcal endocarditis, and the successful combinations were terramycin–streptomycin and penicillin–aureomycin respectively.

These patients afford striking confirmation of one aspect of the Jawetz theory. What evidence is there of the clinical reality of antagonism? Certainly the clearest is the experience of Lepper and Dowling (1951) in the treatment of pneumococcal meningitis. Alternate cases were treated with penicillin alone and with penicillin + aureomycin, the penicillin being given intramuscularly only in a dose of 1,000,000 units two-hourly. Of 14 patients given penicillin only 3 died (21%), and in a total of 43 patients so treated 13 died (30%), whereas only 3 out of 14 receiving combined treatment recovered, a mortality of 79%. A similar though less emphatic conclusion may be drawn from the findings of Lepper *et al.* (1952) in meningococcal meningitis: here there was almost no mortality, but the duration of fever and of "mental abnormality" seems definitely to have been prolonged by combining aureomycin with penicillin. It has been remarked by several authors that conditions in the meninges are ideal for antagonism, critical concentrations for this effect being maintained fairly constantly in an area where efficient bactericidal action is probably imperative. Whether antagonism occurs in other situations it is the task of future clinical observation to decide.

Complexity of the Problem

We have seen that there are several specific instances in which drug combinations are clearly indicated either because they delay the acquisition of bacterial resistance or because they exert a synergic effect. In pyogenic meningitis we have a disease in which certain combinations are contraindicated because their effect is antagonistic, and future clinical appraisal may possibly decide that these combinations are either contraindicated or at least without advantage in other conditions. But these conclusions refer to only a few specific and (except tuberculosis) uncommon infections, and leave the general question of the usefulness of combined therapy in everyday medicine unanswered.

It is strongly emphasized by Jawetz and Gunnison (1952b) that no general rules about synergism and antagonism can be laid down. The same pair of antibiotics may exhibit either effect against different organisms, according to their degrees of sensitivity. Other authors have found that the same pair may be either synergic or antagonistic against the same organism according to the concentrations used. The whole of this account of this subject has in fact been oversimplified, for the sake of brevity, by omitting mention of many factors which have been shown to determine the results of combined action.

In any serious case an *ad hoc* effort to provide a rational basis for treatment should be made by laboratory experiment, and the simplified test of bactericidal action proposed by Martin, Sureau, and Chabbert (1952) may afford useful indications with little delay. On the other hand, more elaborate proceedings may be very advisable, and I calculate that various studies in connexion with our last case of enterococcal endocarditis occupied well over 100 hours of laboratory time. I have contended for many years that the action of chemicals, whether simple germicides or chemotherapeutic agents, on bacteria can be determined in the laboratory in such a way as to provide a reliable guide to their use. I still adhere to this view, but I begin to doubt whether such determinations in connexion with combined antibacterial action are practicable. The feasibility of attaining a significant result from a reasonable amount of any such work depends on the number of variables involved. It might be supposed that the introduction of a second drug merely adds one more variable, and this is true in a sense, but drug interactions are so complex that it does no justice to the result. The bacteriologist who tackles individual problems of this kind seriously is facing what I believe to be the most complicated task in the whole of routine laboratory medicine.

I am indebted to Dr. Bernard Sureau and Dr. Ernest Jawetz for the privilege of reading their papers before publication, and for helpful discussions with both and with colleagues of the former, and to my clinical colleagues, particularly Professor R. V. Christie, for permission to cite their cases.

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CLINICAL TRIAL OF A NEW ORAL DIURETIC

BY

A. G. SPENCER, M.D., M.R.C.P.

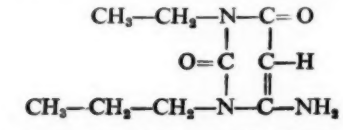
Assistant, Medical Unit,
University College Hospital Medical School, London

AND

H. G. LLOYD-THOMAS, M.B., B.Chir., M.R.C.P.

Assistant Registrar, University College Hospital, London

In a search for a potent non-toxic oral diuretic, Kattus, Newman, and Franklin (1951) tested for diuretic activity in dogs a series of compounds derived from the uracil nucleus. One compound, 1-propyl-3-ethyl-6-aminouracil, was found to be an effective diuretic, and produced only a minor degree of gastro-intestinal disturbance. Papesch and Schroeder (1950) had previously synthesized this substance, and for convenience it is referred to by their serial number, S.C.2614. The structural formula is:



Kattus, Arrington, and Newman (1952) subsequently reported that compound S.C.2614 was an effective diuretic when given by mouth to dogs, to normal human subjects, and to patients with oedema. No serious toxic reactions were noted in their studies.

The present report describes an investigation into the effectiveness of compound S.C.2614 as an oral diuretic when given to normal human subjects and to patients with renal or cardiac disease.

Chemical Methods.—The daily renal excretion of protein was determined by micro-Kjeldahl estimation of the protein precipitate obtained from centrifuged aliquots of the 24-hour urine. The other chemical methods have been described previously (Spencer and Franglen, 1952).

Effect on Normal Subjects

Observations on the diuretic effect of S.C.2614 were made during ten tests on nine normal males aged 21–35 years. These subjects were ambulant and took their normal diet. Urine was collected over two 24-hour periods; the first period being the control day, and the second the test day on which 1,250 mg. of S.C.2614 was taken by mouth in 125-mg. tablets over a period of six hours. The renal excretion of water, sodium, chloride, and potassium was measured on each day, and the results are summarized in Tables I and II.

TABLE I.—*Effect of Compound S.C.2614 on Normal Subjects. The 24-hour Renal Excretion of Water and Sodium on a Control Day Compared with that on a Day when 1,250 mg. of S.C.2614 was Taken by Mouth. Ten Tests on Normal Subjects*

Subject	Renal Excretion in 24 Hours			
	Water (ml.)		Sodium (mEq)	
	Control	S.C.2614	Control	S.C.2614
G.A.	800	2,320	152	260
T.R.B. ..	2,150	3,140	110	251
G.C.	1,210	1,430	179	320
A.M.G. ..	1,730	2,630	157	330
A.B.K. ..	2,355	3,620	167	375
M.N.	1,545	2,410	154	384
G.M.	1,390	2,230	159	210
A.G.S. ..	1,470	2,930	99	303
A.G.S. ..	1,479	2,640	158	457
L.T.	1,600	2,960	196	525

TABLE II.—*Effect of Compound S.C.2614 on Normal Subjects. The 24-hour Renal Excretion of Water and Sodium on a Control Day Compared with that on a Day when 1,250 mg. of S.C.2614 was Taken by Mouth. Means and Standard Deviations of the Data from Ten Tests on Nine Normal Subjects*

	Water (ml.)	Sodium (mEq)	Chloride (mEq)	Potassium (mEq)
Control day ..	1,573 S.D.=460	153 S.D.=29	166 S.D.=32	71 S.D=9
S.C.2614 day	2,631 S.D.=530	341 S.D.=28	378 S.D.=66	97 S.D.=28
Mean difference	+1,058	+188	+212	+26
Mean diuresis as % of control ..	161	222	227	136
Level of significance ..	P=0·01	P=0·01	P=0·01	P=0·02

In nine of the ten tests there was a considerable increase in the urine volume and excretion of sodium and chloride on the test day. One subject did not show a significant water diuresis, although his excretion of sodium on the test day was 178% of that on the control day. For all the ten tests the mean excretions on the test day compared with the control day were: water, 161%; sodium, 222%; chloride, 227%; potassium 136%. In these tests the water diuresis in response to oral S.C.2614 was equivalent to that reported by Blumgart *et al.* (1934) for mercurial diuretics when given by intramuscular injection to normal subjects. The effect of oral S.C.2614 on sodium excretion also compared favourably with that reported by Kattus *et al.* (1952) for a 2-ml. injection of a mercurial diuretic in a comparable series of normal subjects, and was much greater than that which was produced by 1.2 g. of aminophylline by mouth.

Toxic Reactions.—Two subjects complained of epigastric pain and abdominal discomfort, one of anorexia, and two of tinnitus. During the administration of S.C.2614 there was no significant change in the low normal rate of daily excretion of protein in the urine, and in no case did urine microscopy show any abnormality.

Effect on Patients: Method of Investigation

The patients were not deliberately selected, and included those with every degree of fluid retention, from little or no pitting oedema to gross anasarca. Fifty tests were completed on 30 patients, 22 with cardiovascular and 8 with renal disease. All patients were confined to bed and, except when otherwise stated, were given a standard hospital low-salt diet (10–25 mEq) of sodium and a measured fluid intake of 30–50 oz. (850–1,420 ml.). There was a preliminary period of observation of at least six days in which to

detect and exclude those patients who were undergoing a spontaneous diuresis in response to rest in bed and the low-salt diet. Patients treated with digitalis were observed for a longer period, usually one to three weeks, so as to avoid confusion with the diuretic effect of this drug.

TABLE III.—*Effect of Oral S.C.2614 on Patients with Cardiovascular or Renal Disease*

Case No.	Sex and Age	Clinical Condition	Renal Excretion in 24 Hours: Water (ml.) Control Days ±Range	Water (ml.) S.C. Days	Sodium (mEq) Control Days ±Range	Sodium (mEq) S.C. Days
		Cardiac Oedema				
1	F 49	Mitral stenosis, C.C.F., auricular fibrillation, oedema+	(4) 1,090±250	2,500 2,970	9±5	104 79
2	M 71	Aortic regurgitation, C.C.F., oedema+	(3) 760±200	2,200 2,520	5±5	132 214
3	M 73	Aortic regurgitation, C.C.F., oedema++	(6) 1,373±250	2,270	41±10	123
4	F 45	Mitral and aortic stenosis, C.C.F., oedema++, ascites++	(5) 598±200	340	7±5	3
5	F 92	Hypertension, coronary disease, C.C.F., oedema+	(3) 570±100	2,020	16±5	176
6	F 47	Hypertension, coronary disease, no C.C.F., no oedema	(7) 990±200	1,140	5±5	30
7	F 72	Hypertension, coronary thrombosis, C.C.F., oedema++, ascites	(5) 1,365±300	3,980 2,090	22±10	187 79
8	F 57	Hypertension, coronary disease, C.C.F., oedema+	(4) 1,107±250	2,270 1,700 1,820	47±10	123 63 86
9	M 72	Coronary artery disease, C.C.F., oedema+	(6) 825±200	1,530	22±5	26
10	F 55	Hypertension, cardiac asthma, oedema O	(6) 870±250	1,640	14±5	67
11	F 48	Hypertension, cardiac asthma, oedema O	(3) 1,240±1,000	2,400	15±20	36
12	F 70	Hypertension, C.C.F., auricular fibrillation, oedema O	(6) 980±400	1,020	7±5	4
13	F 92	Coronary artery disease, C.C.F., oedema O	(3) 640±50	1,420	17±5	58
14	F 85	Coronary artery disease, C.C.F., slight oedema	(4) 880±400	970	23±5	39
15	M 63	Coronary artery disease, C.C.F., oedema+	(4) 1,345±200	1,380 1,980	18±10	80 76
16	M 46	Coronary artery disease, C.C.F., auricular fibrillation, oedema++	(4) 1,080±200	1,980	7±10	123
17	F 58	Hypertension,? C.C.F., oedema+	(4) 1,500±600	3,070 2,930	54±20	92 83
18	M 64	Hypertension, C.C.F., oedema O	(3) 1,900±200	2,400	8±5	82
19	M 70	Diabetes, coronary thrombosis, C.C.F., oedema++, ascites	(8) 1,260±300	2,470 3,280 1,980 3,060 2,330 2,270	43±10	279 265 98 95 105 107
20	F 48	Constrictive pericarditis, oedema+	(7) 490±400	450 430 1,220	3±5	5 2 3
		Renal Disease				
21	F 67	Diabetic nephrosclerosis, oedema++, blood urea 126 mg./100 ml.	(4) 1,710±200	3,600 3,750	51±10	178 280
22	M 28	Nephrotic stage chronic nephritis, oedema+, blood urea 99 mg./100 ml.	(5) 1,470±250	2,560	10±5	67
23	F 34	Diabetic nephrosclerosis, oedema+, blood urea 136 mg./100 ml.	(6) 1,650±400	2,280	14±5	84
24	M 43	Malignant hypertension, uraemia, oedema+, blood urea 102 mg./100 ml.	(5) 1,036±400	1,440	6±5	8
25	M 52	Chronic nephritis, hypertension, oedema+, ? C.C.F., blood urea 150 mg./100 ml.	(4) 1,360±200	2,980 2,410 2,270 1,990	31±10	200 149 107 117
26	F 28	Nephrotic stage chronic nephritis, oedema+, blood urea 76 mg./100 ml.	(8) 910±200	1,310 910 1,080	6±5	10 4 7
27	M	Chronic nephritis, oedema+++, blood urea 200 mg./100 ml.	(6) 820±250	710	15±5	12

The daily renal excretion of water, sodium, potassium, and chloride ions was measured for three to eight days before the test, on the test day, and for a variable time afterwards. On the test day, starting at 9 a.m., compound S.C.2614 was given by mouth in 125-mg. tablets, two every three hours until 1,250 mg. had been taken. The deposits from the centrifuged urine were examined microscopically in the control period and on the test day. The 24-hour excretion of protein in the urine of 26 patients was also measured.

An approximate comparison of the effectiveness of oral S.C.2614 with a 2-ml. intramuscular injection of mersalyl *B.P.* was obtained by testing both diuretics in 22 patients. There was an interval of at least four days between the two tests, and nine of the patients received the mersalyl injection before the S.C.2614 tablets, while the others were given the S.C.2614 tablets first.

Two tests were invalidated by errors in urine collection, and three patients were given a diet containing approximately 40 mEq of sodium a day, instead of the standard diet containing 10–25 mEq of sodium. The main results of 47 tests, together with a summary of the clinical condition of the patients, are given in Table III.

Assessment of Diuresis

There were formidable difficulties in the assessment of a diuretic response. The test patients differed in the nature of their disease, in the causation of their oedema, in renal function, and in many other variable factors important in the differential distribution of body fluids, such as the concentration of the serum albumin and that of the plasma sodium. Not only did the patients necessarily differ among themselves but there was a considerable variation from day to day in the same patient of the renal excretion of water and electrolytes. This was still the case when the input was constant within the limits of a standard low-salt diet. The prolonged period of observation, necessary to detect and exclude those patients undergoing a diuresis in response to rest and other forms of treatment, produced two further difficulties. First, many patients lost their pitting oedema before the test; and, secondly, the remaining patients with oedema were no longer a representative series, and in fact many were particularly resistant to all forms of treatment. This selection of patients reduced the chance of a successful diuresis in response to compound S.C.2614; but when such a diuresis occurred it could be attributed with more confidence to the drug.

A successful diuretic response has been defined as one in which all the following standards were exceeded on the test day: a urine volume of 70 oz. (1,990 ml.) containing 75 mEq sodium; an excess renal excretion over the intake of 30 oz. (850 ml.) of water and 50 mEq sodium; an excretion of 150% of the mean control values for both water and sodium, with increments greater than four times the mean deviations.

Results in Patients with Heart Disease

Thirty-four tests were completed on 20 patients with heart disease: four with chronic rheumatic carditis and valvular disease, one with constrictive pericarditis, and fifteen with hypertension or disease of the coronary arteries (Table III). The mean results for all the tests on cardiac patients are given in Table IV.

However, these average figures do not represent the true clinical response to compound S.C.2614. The data are abnormally distributed within the series, so that the average figures are misleading. On applying the strict criteria of a

TABLE IV

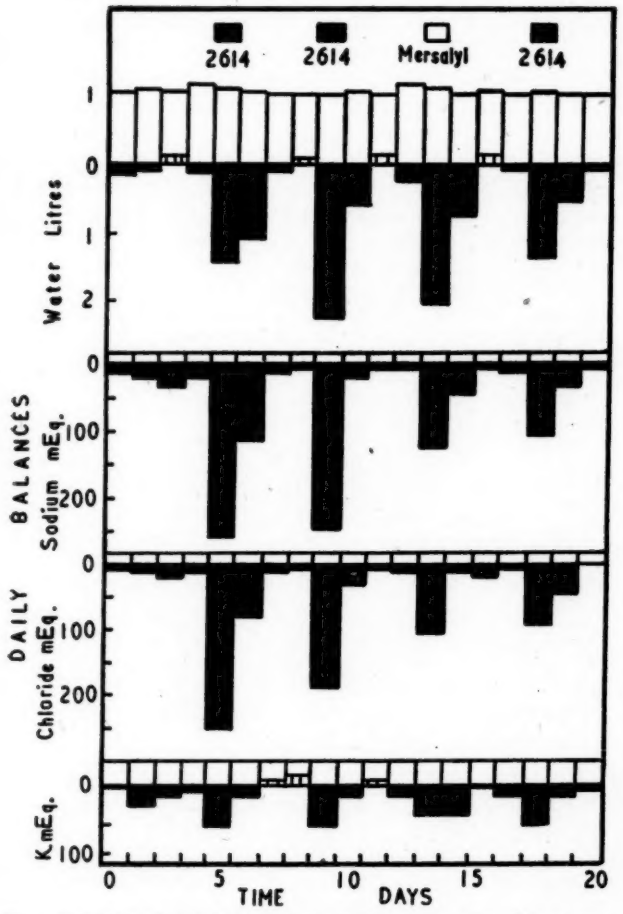
No. of Patients	No. of Tests	Water Excretion: Mean Control	Water Excretion: Mean S.C.2614	Sodium Excretion: Mean Control	Sodium Excretion: Mean S.C.2614
20	34	1,045 ml.	2,040 ml.	27 mEq	92 mEq

TABLE V

No. of Patients	No. of Tests	Successful Diuresis	Water Excretion		Sodium Excretion	
			Mean Control	Mean S.C.2614	Mean Control	Mean S.C.2614
10	22	19	1,070 ml.	2,530 ml.	23 mEq	121 mEq

successful diuretic response which we have previously defined, it is apparent that of the 34 tests 20 were successful; but these 20 successful tests occurred in only 10 patients. This series has therefore been subdivided into three groups:

(*a*) *Oedematous Patients Without Evidence of Sodium Depletion* (Table V).—The diuretic response to S.C.2614 in this group of patients was very satisfactory, and, as will be shown later, the results were comparable with those obtained from intramuscular mersalyl. An example of a successful series of diuretic responses is given in the accompanying Chart.



The effect of oral S.C.2614 and of intramuscular mersalyl (2 ml.) on an oedematous patient with congestive cardiac failure. The daily balances of water, sodium, potassium, and chloride ions. Intake 20 mEq sodium and 1,000–1,200 ml. of water a day. Input plotted upwards from the base lines and output downwards from the level of the input, so that the black columns represent the daily negative balances.

(*b*) *Oedematous Patients with Sodium Depletion.* (Plasma sodium below 132 mEq, or a recent large abdominal paracentesis.) (Table VI).—There was no successful diuretic response in this small group of patients. One subsequently had a good diuresis following an injection of mersalyl.

TABLE VI

No. of Patients	No. of Tests	Failures	Water Excretion		Sodium Excretion	
			Mean Control	Mean S.C.2614	Mean Control	Mean S.C.2614
2	4	4	540 ml.	605 ml.	5 mEq	3 mEq

(*c*) *Patients Without Pitting Oedema* (Table VII).—Although none of this group of patients had a good diuresis in response to oral S.C.2614, there was a noticeable effect on water and sodium excretion. This was approximately half of that obtained in those patients with oedema and no evidence of sodium depletion.

TABLE VII

No. of Patients	No. of Tests	Failures	Water Excretion		Sodium Excretion	
			Mean Control	Mean S.C.2614	Mean Control	Mean S.C.2614
8	8	8	992 ml.	1,537 ml.	13 mEq	53 mEq

Comparative Efficiency of Oral S.C.2614 with Intramuscular Mersalyl

Because patients differed widely in their response to a single diuretic, and as the response of the same patient also varied from day to day, it was extremely difficult to obtain a reliable comparison of the relative effectiveness of two different diuretics. In the twin tests of oral S.C.2614 and intramuscular mersalyl (2 ml.) the order in which the diuretics were tested obviously affected the result (Table VIII).

TABLE VIII.—*Efficiency of Oral S.C.2614 Compared with a 2-ml. Intramuscular Injection of Mersalyl in Patients with Cardiac Disease*

	No. of Tests	S.C.2614 Mean Diuresis			Mersalyl Mean Diuresis		
		Water (ml.)	Sodium (mEq)	Successes	Water (ml.)	Sodium (mEq)	Successes
Mersalyl first..	9	1,760	43	4	2,353	97	8
S.C.2614 first..	13	2,146	81	8	2,173	63	5

When mersalyl was given first it produced twice as many successful diuretic responses as did the subsequent tests of S.C.2614, and the mean excretion of water and of sodium in response to mersalyl was much greater. When compound S.C.2614 was tested first it produced eight successful diuretic responses compared with five by mersalyl, but the mean excretion of water and sodium was of the same order for both diuretics. For both groups of tests the mean excretion of water and of sodium was, for mersalyl 2,260 ml. of water and 80 mEq of sodium; for S.C.2614 1,950 ml. of water and 62 mEq of sodium. It appeared, therefore, that although compound S.C.2614 was an effective diuretic in the oedematous patients it was not generally such a potent diuretic as a 2-ml. intramuscular injection of mersalyl.

This conclusion is supported by a comparison of the data available for compound S.C.2614 with those published for mercurial diuretics in patients with heart disease (Table IX). The approximate relative efficiency of various diuretics compared with intramuscular mercurials (100%) appears to be: intravenous mersalyl, 120–140%; mersalyl suppositories, 40%; "novurit" suppositories, 80%; oral "unephral"

TABLE IX.—*A Comparison of the Response to Various Diuretics in Patients with Heart Disease. Urine Volumes (ml.) on the Test Day*

Oral S.C.2614	Oral Mercurials	Mercurial Suppository	Intramuscular Mercurials	Intravenous Mersalyl
1,960[1]	Mersalyl 1,500[3]	1,350[3]	2,190[4]	3,000[3]
1,950[2]	Unephral 1,876[3]	2,360[4] (novurit)	2,500[3]	2,860[4]
2,530[2a]				
*70–110%	*60–70%	*40–80%	*100%	*120–140%

[1] Kattus *et al.* (1952) all cases.
[2] Present series, all cases.
[2a] Present series, oedematous cases.
[3] Calculated from Evans and Paxton. (1941).
[4] Thomson (1937).
* Approximate efficiency compared with intramuscular mercurial diuretics used with theophylline and ammonium chloride.

(formerly "neptal"), 70%; oral mersalyl, 60%; oral S.C.2614, 70–110%. The mercurial diuretics contained theophylline and were given in conjunction with ammonium chloride.

Results in Patients with Renal Disease

There were 13 tests of compound S.C.2614 on seven patients, and in only two was there a successful diuretic response (Table III). Two successful responses were obtained from a patient with diabetic nephrosclerosis, and four from a patient with chronic nephritis, but the oedema in the latter case was probably produced in part by congestive heart failure.

Toxic Reactions to Oral Compound S.C.2614

Gastro-intestinal disturbances were reported by 9 of the 39 subjects who were given compound S.C.2614. The complaints were: epigastric discomfort, 9; anorexia, 8; nausea, 7; vomiting, 4. Apart from the four patients who each vomited on a single occasion, the symptoms were mild and did not interfere with the administration of the tablets.

Two normal subjects complained of tinnitus. One patient had a transient sparse urticarial eruption.

Routine microscopy of the urine did not show any alteration in the pattern of the organized deposit following the administration of S.C.2614.

Patients with gross albuminuria often showed a pronounced increase in the 24-hour excretion of urinary protein on the day in which S.C.2614 was given.

Comment

The therapeutic value of a new drug, and its toxic effects, can be assessed only by a prolonged study of its action on a large number of patients. Such a large-scale clinical trial would be justified by the unqualified success of the drug in a pilot experiment. The present trial of S.C.2614 appeared to show that, in a divided dose of 1.25 g., it was an effective oral diuretic in 70% of patients with cardiovascular disease, provided there was definite oedema and no evidence of sodium depletion. In this group of patients oral S.C.2614 was usually about 80% as effective as a 2-ml. intramuscular injection of mersalyl, preceded by ammonium chloride. There was seldom a useful diuretic response to S.C.2614 in the absence of oedema or in patients who had a low plasma sodium, a serum albumin below 2 g. per 100 ml., or a blood urea over 150 mg. per 100 ml. Intramuscular mersalyl was also generally less effective in these patients, but usually more successful than S.C.2614. There was not enough evidence to assess the value of S.C.2614 in patients with renal disease, but there were some good diuretic responses.

This useful diuretic action of S.C.2614 was seriously offset by the high incidence of gastro-intestinal disturbance following the ingestion of the tablets. Although these symptoms were rarely severe, they were sufficient to elicit a spontaneous complaint from 23% of the test subjects. We have therefore begun a pilot trial of a related aminouracil compound which is believed to be less toxic that compound S.C.2614 (Winter, personal communication). For these reasons it is thought that extensive trials of compound S.C.2614 are not justified at the present time.

An effective non-toxic diuretic would undoubtedly be useful in domiciliary practice and when the mercurial diuretics are contraindicated. Further studies of the aminouracil compounds may therefore be profitable, either by themselves or in conjunction with other diuretics.

Summary

A new oral diuretic, an aminouracil compound designated S.C.2614, was tested 57 times in 36 subjects in a divided dosage of 1.25 g.

In normal subjects there was a satisfactory diuresis in nine out of ten tests. Expressed in relation to the mean excretion on the control days the mean diuresis was: of water, 161%; sodium, 222%; chloride, 227%; and potassium, 136%.

In 22 tests on 10 oedematous patients with heart disease there was a good diuretic response in 19, with a mean urine volume of 2,530 ml. containing 121 mEq of sodium; water excretion 236%, and sodium 520% of the control days. This was 80% of the diuretic effect of a 2-ml. intramuscular injection of mersalyl *B.P.* in the same group of patients.

Compound S.C.2614 usually failed to produce a satisfactory diuresis in any other group of patients. There were 19 failures in 25 tests on 17 patients. No useful diuresis occurred in cardiac patients without pitting oedema, in patients with a low plasma sodium, a serum albumin below 2 g. per 100 ml., or a blood urea over 150 mg. per 100 ml.

There was not enough evidence to assess the effect of S.C.2614 in patients with renal disease, but there were a few useful diuretic responses.

The high incidence (23%) of gastro-intestinal disturbance provoked by S.C.2614 was regarded as a serious disadvantage, although such symptoms were usually mild.

Further studies are in progress with a related aminouracil compound which may prove to be less toxic than S.C.2614.

We gratefully acknowledge the help given by Professor M. L. Rosenheim and the physicians of University College Hospital; by the nursing staff, the normal test subjects; by Mr. G. T. Franglen, who did some of the earlier chemical estimations; and by Dr. Irwin C. Winter, of G. D. Searle and Co., for information and supplies of the aminouracil diuretics.

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Since the publication of the Curtis Report (1946) and the carrying out of its recommendations for children "taken into care," increasing attention has been given to children neglected or ill-treated in their own homes. The National Association for Maternity and Child Welfare, in collaboration with other bodies, has issued a short report, *Child Neglect and the Social Services*, on the present position and future possibilities for dealing with child neglect or ill-treatment in the home. It is estimated that the 80,000 problem families in England and Wales contain upwards of 250,000 children. A joint circular issued by the Home Office and the Ministries of Health and Education in 1950 drew attention to the powers of local authorities under the Children Act, the National Assistance Act, and the Education Acts. The circular suggested that officers should be designated to be responsible for enlisting the interest and co-operation of local services concerned with the welfare of children in their homes, that these officials should meet regularly officers of local authorities and other responsible organizations, and that cases of child neglect and ill-treatment should be reported to the designated officer. The report is obtainable from the National Association for Maternity and Child Welfare, at Tavistock House North, Tavistock Square, London, W.C.1, price 2s.

CONTROLLED HYPOTENSION IN NEUROSURGERY WITH HEXAMETHONIUM AND PROCAINE AMIDE

BY

DAVID ASERMAN, M.D., D.A.

Anaesthetist, the National Hospital, Queen Square, London

The two greatest difficulties with which the neurosurgeon has to contend are haemorrhage and increased intracranial tension. It is now becoming possible for the anaesthetist to give him the great advantage of working in an almost bloodless field and with a brain shrunken to an easily manageable size; but these benefits are bought at the price of certain dangers. This paper attempts to outline the methods of lowering the blood pressure, to give a list of the main dangers that may be encountered, and to suggest measures for countering them.

Methods of Controlling Blood Pressure

Hexamethonium Bromide (or Iodide).—This is the drug in common use for the induction of hypotension. Its great disadvantage is that it has a failure (or partial failure) rate of some 40%.

Procaine Amide.—This is used extensively in cardiac and thoracic surgery for the elimination of cardiac irregularities. A common side-effect is to cause a slight lowering of the blood pressure, and W. D. M. Paton (personal communication) has suggested that this may be due to a weak ganglion-blocking effect. There often follows a small decrease in the pulse rate, which connotes possibly a decrease in cardiac output. When a case fails to respond satisfactorily to hexamethonium a suitable dose of procaine amide will with a high degree of probability convert it into a successful case of hypotension. The reason for this potentiation is not clearly understood. It may be due to a simple synergistic action or to the effect of a reduced cardiac output, or to a combination of these factors.

Posture.—This plays an important part in the management of the case. Before the administration of the hypotensive drug the patient is placed in an anti-Trendelenburg tilt of 25 to 30 degrees. This will usually reduce the blood pressure by about 10 mm. Hg. The tilt is decreased during the course of the operation if the blood pressure falls too low. Post-operatively the blood pressure is prevented from rising too rapidly or from falling too low by altering the position of the patient. As an example of the delicacy of blood-pressure control by means of posture, we operated on a few cases on a table which did not have a foot-rest (to prevent the patient sliding down the table). The patients were arranged with the head slightly raised, the body almost horizontal, and the legs hanging over the end of the table. In each case when it became necessary at the end of the operation to increase the blood pressure the mere act of raising the legs to the horizontal position caused a rise of 15 to 20 mm. Hg within a few minutes. In only two cases has it been necessary to resort to methylamphetamine hydrochloride to raise the blood pressure post-operatively.

Dangers of Hypotensive Anaesthesia

1. Allowing the Pressure to Drop too Low

It cannot be said with certainty how low the pressure may be dropped with safety. Pressures below 60 mm. may result in liver damage. Still lower pressures may be associated with anoxia, thrombosis, or even death. One fatal case probably falls into this category, but with the added results of "retractor anaemia," under which heading it is described.

2. Anoxia

Although there is no supporting evidence, it is possible that a slight degree of cerebral anoxia may be present during hypotension because of the reduced amount of blood passing through the brain. The colour of the brain and blood does not suggest that this is so. Siguier *et al.* (1951) state that the electroencephalogram shows no evidence of anoxia. During direct electroencephalographic recordings of the cortex I have deliberately produced a slight degree of anoxia (without hypotension), and the tracings have shown no changes from the normal. The claim of Siguier *et al.* would therefore seem to be valueless. Nor do tracings under hypotension show variations from the normal. There is evidence to suggest that the blood flow through the brain is less than is indicated by the brachial blood pressure, and that therefore the danger of anoxia may be greater than would appear on the surface.

A man of 20 was having his frontal lobe amputated for epilepsy. His blood pressure before operation was 126/84. An inexplicable rise to 160/120 after induction was lowered to 154 by 50 mg. of hexamethonium, and to 134 by a further dose of 50 mg. All this time, as was to be expected, a good deal of bleeding was going on and the dura was tense. At this stage 400 mg. of procaine amide was given intravenously, and within a few minutes the bleeding had stopped and the brain had retracted from the dura. Yet the blood pressure was 118.

It is hoped to obtain further knowledge on this point by taking blood pressure readings from a cerebral artery. No definite evidence of anoxia has appeared in any cases in the present series, yet its results may possibly have been masked by surgical trauma.

3. Thrombosis

This is an ever-present danger and may occur with even a small drop in blood pressure. Many cases have been reported under this form of anaesthesia. There were no cases of thrombosis in the present series.

4. Reactionary Haemorrhage

In general surgery, under hypotension, reactionary haemorrhage has been one of the most frequent complications. In neurosurgery it is apt to occur under any type of anaesthesia. It has occurred in only one case in this series.

A woman of 54 had an angioma removed in the morning. After an early recovery she became drowsy towards evening and showed signs of intracranial bleeding. On reopening the flap a small subdural clot, together with a quantity of blood-stained fluid, was evacuated. The surgeon felt doubtful whether this was a true haemorrhage. The patient had no further trouble and made a good recovery.

5. "Retractor Anaemia"

So far as I know this condition has not up to the present been recognized, and for that reason and because of its importance it is dealt with at some length. In the series there were three deaths attributable directly or indirectly to the anaesthetic. All three showed evidence of "retractor anaemia," two of them to a marked degree.

When hypotension is induced the brain retracts within the cranial cavity, leaving a clear space between it and the cut edge of the dura. At the same time its consistency is completely altered. It has lost all tone and behaves like soft dough. When pressure is applied it is easily compressed, and on release is slow to regain its normal conformity. Blood is forced out of those parts of the brain on which the pressure is exerted, and because of the small blood flow the vessels are only slowly replenished on removal of the pressure. It can be seen that pressure by a brain retractor may be transmitted even to comparatively

distant parts of the brain, thereby depriving those areas of their blood supply and thus causing irreversible and possibly widespread damage.

A man of 35 had a pituitary adenoma removed. He recovered well from the operation and anaesthetic and was responding within a few minutes of the end of the operation. His condition continued to be satisfactory, giving no cause whatsoever for anxiety, when suddenly, eight hours later, he died. The post-mortem findings were: "Cranium and contents: Haemorrhage had taken place around the bone-flap and no haemorrhage was present under the dura. The convolutions of the cerebral hemisphere was flattened and there was some herniation of the right hemisphere under the falx. A marked degree of tonsillar herniation through the foramen magnum had occurred. . . . . Haemorrhage had taken place into the remaining portions of the tumour and into the right frontal lobe. The right frontal lobe was soft in consistency. The right cerebral hemisphere was greatly enlarged, particularly anteriorly, and herniated under the falx. . . ."

The striking part of this report is the great enlargement of the right hemisphere, particularly the anterior part of it—so great, in fact, that part of the lobe had to be accommodated under the falx. (The craniotomy was of course performed on the right side.) The enlargement is undoubtedly due to acute oedema, which, in its turn, is caused by vascular damage. Had vascular damage been caused by hypotension and anoxia due to the anaesthetic one would have expected enlargement of both hemispheres. There seems, therefore, little room for doubt that the damage was caused by retractor pressure. A second death occurred in the following case.

A man of 42 with a right frontal glioma had had his frontal lobe amputated. Post-operatively he did not regain consciousness, and died the following morning. His blood pressure, by an unfortunate chain of circumstances, had been allowed to remain too low, and at the time we attributed his death to this cause. The post-mortem examination showed: "Cranium and contents: no evidence of thrombosis was seen in the venous sinuses. The convolutions of both cerebral hemispheres were flattened and the sulci shallow. The right hemisphere was much larger than the left and had herniated under the falx cerebri. It filled the cranium, although the frontal lobe had been amputated for the removal of a calcified glioma. On the right the hippocampus herniated through the tentorium cerebelli, pushing the right communicating artery downwards, and portions of the hippocampus lay on either side of the vessel. There was no marked degree of tonsillar herniation. A large amount of blood had collected in the cisterna magna. The right frontal lobe had been amputated, but the right hemisphere filled the cranial cavity on this side and herniated to a very marked degree under the falx. . . ."

Here we have a picture very similar to the previous case. Amputation of the frontal lobe is a comparatively innocuous procedure which as a rule causes little or no upset to the patient. A persistent low blood pressure would be expected to cause more generalized changes in the brain. The pronounced changes on the right point once again to the extreme vulnerability of the brain, in the hypotensive state, to retractor pressure. A third death occurred in the following case.

A man of 39, with a pituitary adenoma, was one of the early cases in the series; we were then not seriously concerned if the blood pressure fell to below 60. In this case it dropped to 40, and, in spite of reducing the tilt, did not rise more than a few points. He failed to come round after the operation, developed decerebrate rigidity, and died the following day. A post-mortem examination revealed the following: "On removing the skull vault the dura was under marked tension and the underlying brain obviously swollen. . . . On cutting the brain there was marked oedema throughout both hemispheres. . . ." Pathological report: ". . . Examination revealed a haemorrhage 2 cm. in diameter situated at a low level in the right cerebral peduncle. . . ."

Bilateral enlargement of the hemisphere suggests generalized brain damage by too low blood pressure. The haemorrhage into the peduncle may have been caused by retractor pressure. Several of the earlier cases were operated on under very low pressure without obvious ill effects, and, while this is no argument that the patient did not die as a result of the damage due solely to low blood pressure, retractor pressure cannot be entirely dissociated as an additional factor.

An interesting comparison with the preceding examples is provided by a case which terminated fatally, a result for which the anaesthetic could in no way be held responsible.

A woman of 56 was being operated on for removal of a sphenoid wing meningioma. In the course of the operation the surgeon accidentally opened a big vessel, causing a profuse and rapid loss of blood. In due course the haemorrhage was arrested by clipping two large arteries. During this period the condition of the patient had been fairly satisfactorily maintained by rapid replacement of blood and, of course, by levelling the table. By the end of the operation she was responding well and her general condition was quite good. However, she gradually deteriorated, and died the same day. The necropsy report was as follows: "The cerebral convolutions of both hemispheres were flattened. The right cerebral hemisphere was enormously enlarged and had herniated under the falx cerebri. The adjacent sides of the fronto-temporal lobes had been removed. The fronto-parietal part of the hemisphere was very soft in consistency. Clips were present on the right middle and right anterior cerebral arteries. A considerable degree of hippocampal herniation had taken place on the right side. . . . An extensive infarction was present in the region supplied by the right middle cerebral artery. . . . The hypothalamus on the right side did not appear to be infarcted. . . ."

This picture is strikingly reminiscent of the previously described cases. Each shows the result of widespread ischaemia of the brain, in one case by clipping arteries, in the other cases by retractor pressure on the brain.

Two cases of pituitary adenoma show post-operative signs which may have been due to retractor pressure. As a rule these patients proceed to an uneventful recovery.

A man of 49 made a good immediate recovery, but had a stormy convalescence. On discharge the final note read: "This man has made an excellent recovery following aspiration of a cystic chromophobe adenoma; however, he remains retarded and still has pathological extensor plantar responses. Post-operatively he has some ataxia of his gait and left arm."

A man of 64 was in coma for two hours after operation. He remained drowsy and incontinent after initial improvement. The final note said: "He is alert, fully orientated as regards time, place, and person. He remains, however, quite still, a little sleepy, more than normal."

Technique

Premedication consists of atropine only, given half an hour to an hour before operation. The patient is induced with thiopentone, 0.5 to 1 g., followed by a short-acting relaxant and 50 to 100 mg. of pethidine intravenously. An endotracheal tube is then introduced and anaesthesia is maintained on a nitrous oxide and oxygen mixture with periodic injections of 15 to 20 mg. of pethidine. Rarely, very small quantities of trichlorethylene are added.

Of the relaxants I prefer gallamine triethiodide to succinylcholine chloride, as the duration of action of the latter is so short that introduction of the endotracheal tube will often start a bout of coughing. Gallamine triethiodide allows time for the pethidine to come into action, so that one is rarely bothered by this disturbance. Succinylcholine chloride has the advantage so far as relaxation of the cords is concerned.

In all craniotomies an intravenous drip is put up; in cases in which excessive haemorrhage is anticipated the drip is duplicated. The patient is placed on the operating table, which is then put into an anti-Trendelenburg tilt of 25 to 30 degrees. The head is cleaned and draped, and at this point the hexamethonium compound is injected. If a local analgesic is used, adrenaline must of course be omitted, as it antagonizes the action of hexamethonium.

In certain operations—namely, hemispherectomy or excision of an epileptic focus—the actual operation of ablation is preceded by direct electrical stimulation of the motor cortex and electroencephalographic tracings. Since these investigations involve a considerable amount of time the hexamethonium is withheld until these procedures have been completed.

Neither pethidine nor hexamethonium has any effect on the electroencephalogram, in contradistinction to thiopen-

tone, which, in small doses, potentiates epileptic waves and is given when it is desired to produce this effect.

Enderby and Pelmore (1951) suggest initial doses of 40 to 50 mg. of hexamethonium. Guiot and Damoiseau (1952) postulate a maximum of 50 mg. I have found these doses to be on the low side, and originally my practice was to start with at least 100 mg. in a robust patient, and I have at times increased this to as much as 250 mg. When using procaine amide in addition for resistant cases I am now giving rather smaller initial doses of hexamethonium—40–75 mg. for an elderly patient, 50–100 mg. for a young adult.

Within a few minutes of the injection the blood pressure will begin to fall and in a favourable case will reach a point between 60 and 70 mm. Hg, where it will remain. At the same time the pulse pressure shows a considerable decrease with only a few points marking the difference between the systolic and the diastolic pressure.

As a general rule bleeding is minimal when the pressure is dropped to 70 or lower. This is surprising, as one would expect that in order to obtain what would appear to be this critical point in bleeding it would be necessary to produce a lower blood pressure in a patient with an initial low pressure than in a patient with an initial high pressure. A blood pressure below 60, we now know, may result in liver degeneration. Our aim should therefore be to keep the pressure between 60 and 70.

Frequently, following the injection of hexamethonium, the initial fall in blood pressure, which may reach a point well below 60, is quickly followed by a rise which, favourably, will be held below 70. If the pressure should remain below 60 for more than a few minutes the foot-down tilt must be decreased until this pressure is attained. If, on the other hand, the pressure should continue to rise beyond 70, increasing the tilt will not check the rise. Nor will an additional dose of hexamethonium as a rule have the desired effect. Yet again hexamethonium may fail to give a satisfactory response in the first place, and the pressure may drop by only a few points.

The cases in which hexamethonium fails to give an adequate reaction or in which the action is of extremely short duration constitute a fairly high proportion of the total number—in the neighbourhood of 40%—and until recently they were therefore written off as failures. With procaine amide at our disposal we are now able to "rescue" the majority of them.

The dose of procaine amide is judged according to the previous effect of the hexamethonium and the age and condition of the patient, and varies between 200 and 500 mg. A poor result of hexamethonium demands a high dosage of procaine amide, as does a young and robust adult.

Assuming the hexamethonium has been given, one should be able to decide within five to seven minutes whether a successful reaction is to be anticipated. If after this time the blood pressure fails to reach a satisfactory level, or, having dropped to a suitable level, immediately begins to rise and continues to do so, procaine amide should be given. The injection is made intravenously and slowly, taking ten to twenty seconds for each 100 mg. From now on there is no further tendency for the blood pressure to rise. It will remain stationary for ten minutes or so and then gradually fall. At the same time there will usually be a decrease in the pulse rate.

One cannot predict the duration of action of these compounds. A single dose will often suffice for the complete operation. On the other hand, if the blood pressure rises, causing increased bleeding, the drug will have to be given again. The second dose should be much smaller than the first.

At the conclusion of the operation Siguier *et al.* raise the blood pressure by rapidly returning the patient to horizontal, and all bleeding is then stopped. Our policy from the beginning has been to allow a slow return of blood pressure over several hours. This is carried out entirely by means of posture. The nursing staff have clear instructions that the blood pressure must, so far as possible, be kept below 100 for several hours.

Recovery

Recovery from the anaesthetic is usually extremely good and very similar to recovery after pethidine anaesthesia. Hexamethonium, in fact, seems to have little added effect. Provided the blood pressure is over 70, consciousness is regained within a few minutes after the end of the operation and the patient will respond to simple commands and answer simple questions, albeit drowsily.

Post-operative restlessness is uncommon, owing, no doubt, to the action of pethidine, which allows a prolonged period of freedom from pain and headache and thus eliminates to a great extent the need for post-operative sedative drugs.

The patient can easily be roused, and there is no danger of confusing this drowsiness with that due to post-operative bleeding.

Contraindications

As thrombosis is one of the chief dangers with this form of anaesthesia, any pre-existing liability to thrombosis would be a contraindication to its use. Unfortunately we are unable to assess this liability, particularly in the case of coronary disease. A previous coronary thrombosis is, of course, an absolute contraindication.

Guiot and Damoiseau give hypertension and arteriosclerosis as contraindications. I should be very chary of employing the method in an advanced case of arteriosclerosis, but early cases, as one would expect, react well to the drugs and do not appear to come to harm.

I have used the method in a number of children, most of whom have reacted favourably. A child of 3 failed to give a satisfactory response, whereas a perfect result was obtained in a 7-years-old child. Comparatively large doses are required in children. The oldest patient was a man of 70.

With the danger of "retractor anaemia" in mind, it follows that this method of anaesthesia is absolutely contraindicated in any operation in which pressure is applied to a portion of the brain that is not to be excised in the course of the operation. There are occasions when it is impossible to decide in advance whether such pressure will be necessary, and in these cases it is advisable to defer the induction of hypotension until the bone flap is turned and the surgeon is quite clear about the condition he has to deal with. In this respect it is the surgeon's responsibility to decide whether hypotension is suitable or not.

When operations in the posterior fossa are carried out with patients in the prone position the same rule will apply. In this unit, however, these operations are performed in the sitting-up position, in which operating conditions are as a rule satisfactory, as regards both haemorrhage and intracranial tension. It would, of course, be foolhardy to use a hypotensive drug with a patient in this position.

Descriptive Cases

A few unusual cases are of interest.

A woman of 50 had a cerebrospinal leak from the anterior fossa. Before the opening was successfully sealed off, three operations were performed at intervals of six weeks and fourteen weeks. In each of the first two operations 150 mg. of hexamethonium produced a perfect result. In the third operation 80 mg. sufficed. The blood-pressure charts were almost identical in the three operations.

A woman of 43 with an angioma had two operations within 11 days. In the first an initial drop in blood pressure with 80 mg. of hexamethonium was followed by a slow rise which necessitated the injection of 300 mg. of procaine amide. The blood pressure fell to 66, where it remained throughout operation. At the second operation 100 mg. of hexamethonium reduced the pressure

to 50, but it rose steadily throughout the operation, which lasted only half an hour. There was a steady blood loss towards the end of the operation.

Two points emerge from these cases. First, it would seem that a patient who once responds satisfactorily to these drugs may be expected to respond in the same way on any future occasion. That being so, the converse is of course true. Secondly, hexamethonium alone may at times suffice for a short operation. If the operation is more prolonged additional hexamethonium may be given, but probably procaine amide will have the more lasting effect.

A man of 70 was being operated on for removal of a meningioma. Thirty-seven minutes after induction with thiopentone, gallamine triethiodide, and pethidine he developed an attack of asthma. Some 10 minutes previously he had been given an injection of hexamethonium, which had reduced his blood pressure to 66. Surprisingly the supervention of bronchospasm failed to cause an appreciable increase in blood pressure and the bleeding remained negligible and the colour good; but movements of the head due to laboured breathing and bulging of the brain during expiration were an annoyance to the surgeon. The condition persisted throughout the operation, clearing up within a few minutes after withdrawal of the endotracheal tube. The patient made a good recovery.

Results

The series consists of 90 cases. I have divided these into two groups, which happen to be equal in number; the first includes all those cases up to the time when procaine amide was first used, the second the remainder. The criteria of success were a negligible amount of bleeding and a good reduction in intracranial tension. Many cases, while not completely fulfilling these criteria, gave unquestionably improved operating conditions, and these I have classified as "partially successful."

In the first group of 45 cases 26 (58%) were successful, 9 (20%) were partially successful, and 10 (22%) were failures. In the second group 38 (85%) were successful, 5 (11%) were partially successful, 2 (4%) were failures.

It will be seen from these figures that procaine amide is a useful adjunct to this form of anaesthesia, as it converts many of the potentially failed and partially failed hexamethonium cases into successful ones.

Three deaths due directly or indirectly to the anaesthetic have occurred. In the light of our experience two at least of these cases are considered to have been unsuitable for this type of anaesthesia.

There was one case of reactionary haemorrhage.

Summary

The advantages of controlled hypotension in neurosurgery are listed.

The dangers of the method are discussed, with special reference to "retractor anaemia."

A method is described of reducing the failure rate of hexamethonium by potentiating with procaine amide.

The results of a series of 90 cases are given.

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The *Hebrew Medical Journal* (Harofé Haivri) recently completed its twenty-fifth year of publication. Although it has been edited and produced in the United States, much of its contents have been published in Hebrew. It is a remarkable achievement on the part of those concerned that they have succeeded in adapting so ancient a language to the needs of modern medicine and have created a medical terminology and literature in Hebrew. The present editor is Dr. Moses Einhorn.

AN OUTBREAK OF DIPHTHERIA: INFLUENCE OF IMMUNIZATION

BY

C. D. L. LYCETT, M.D., D.P.H.

Deputy County Medical Officer of Health and Deputy School Medical Officer, Staffordshire

AND

J. T. A. GEORGE, M.B., Ch.B., D.P.H.

Medical Officer of Health, Coseley Urban District

During 1951 an outbreak of diphtheria of unusual size for the present time occurred in and around Coseley. Coseley, with a population of 34,414 at the 1951 Census, is an urban district in the Administrative County of Stafford between the county boroughs of Wolverhampton and Dudley and almost surrounded by other industrial districts. Wolverhampton and Dudley were not included in the investigation here considered, but it is understood that Wolverhampton had five cases of diphtheria during the year and that Dudley had 11 (all during the first two quarters). The total population of the seven surrounding districts included in this report was 232,836, and together they had 50 confirmed cases during the year, while Coseley had 58. These 108 cases were 15.5% of the 699 (provisional) corrected notifications for England and Wales in 1951. There has in the past been a steady and at times surprisingly high incidence of diphtheria in the neighbourhood. In Fig. 1, the figures for which were obtained from the annual reports of the medical officers of health of Coseley, the number of notifications and deaths and the population for the years 1908–51 are given.

The incidence of diphtheria in Coseley in recent years compares unfavourably with the national incidence and that of non-county boroughs and urban districts (England only, excluding London), as is shown by Fig. 2, which is based on figures published in the Registrar-General's statistical reviews 1912–49.

Bacteriology

The bacteriology of diphtheria in the Administrative County of Stafford is of interest.

Menton *et al.* (1935) reported the results of 500 swabs from 500 individual patients classified according to the type of diphtheria organism; their figures showed a marked predominance of mitis diphtheria. For 1941–4 the published data of the Stafford Public Health Laboratory showed a change to the gravis and, to a lesser extent, to the intermedius types. Comparable figures for 1946–50 show that the intermedius type exceeded the gravis type, which, however, still almost equalled the mitis type in number. In 1951 the outbreak was due to gravis diphtheria. The data are set out in Table I.

TABLE I.—*Relative Incidence of Types of C. diphtheriae—Administrative County of Stafford (Based on the Number of Cases Shown in Parentheses)*

	Reported in 1935	1941–4	1946–50	1951
Gravis	3·8% (19)	56·9% (1,230)	27·0% (98)	98·7% (78)
Mitis	68·6% (343)	6·7% (144)	27·5% (100)	1·3% (1)
Intermedius ..	19·8% (99)	36·4% (787)	45·5% (165)	0% (0)
Irregular ..	7·8% (39)	— (—)	— (—)	— (—)

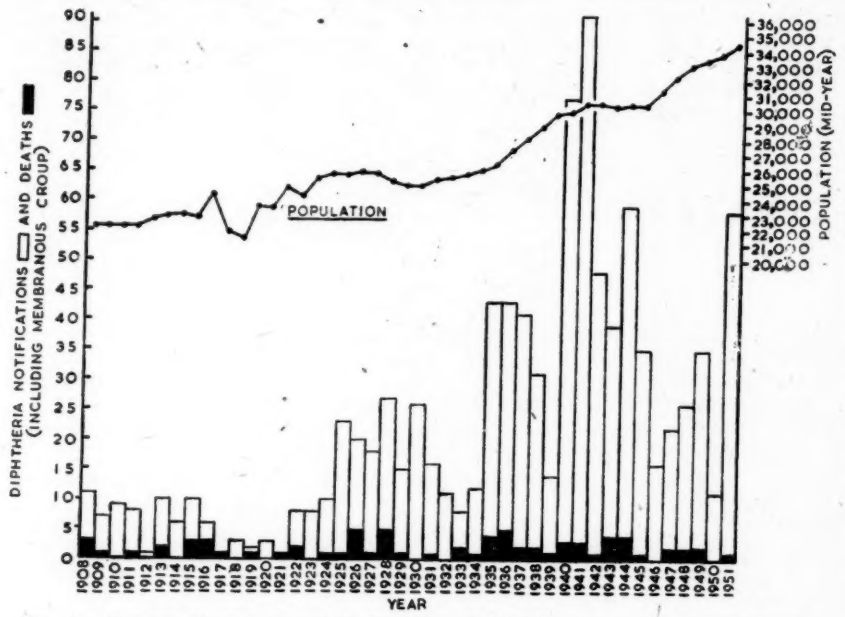

FIG. 1.—Number of cases of and deaths from diphtheria, and population in Coseley for 1908–51.

Logan (1952) considers that the general rapid downward trend in diphtheria cases and deaths in England and Wales may be partly due to the fact that the proportion of mitis strains recovered between 1945 and 1948 almost doubled, whereas the proportions of intermedius and gravis strains substantially declined. Although this change of type occurred in Staffordshire between 1945 and 1948, it was not accompanied by a marked reduction in the incidence of diphtheria, and over the longer period 1935–51 the change in type has been the opposite.

In Coseley, in 1951, swabs from 77 persons (not all confirmed clinical cases of the disease) were positive on culture for the diphtheria organism, and they were all of gravis type with the exception of one of intermedius type. The corresponding figure for the surrounding districts was 28—all gravis. Comprehensive records of swab results obtained in the years 1936–40 are unfortunately not available; therefore the precise period during which the change of type occurred is not known, nor can a hypothetical reason for the change be offered. Fig. 1 shows that the present wave of diphtheria was already well established in 1935, 1936, 1937, and 1938, and that the death rate was as high in 1936 as at any time since.

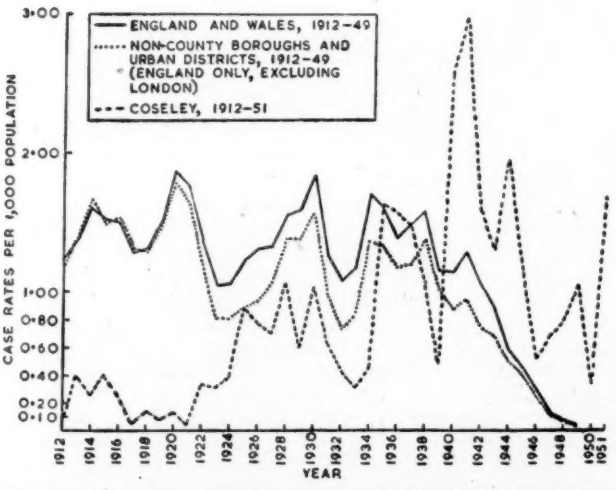
ENGLAND AND WALES, 1912–49
NON-COUNTY BOROUGHS AND URBAN DISTRICTS, 1912–49 (ENGLAND ONLY, EXCLUDING LONDON)
COSELEY, 1912–51
CASE RATES PER 1,000 POPULATION
YEAR

FIG. 2.—Incidence of diphtheria in England and Wales, in non-county borough and urban districts (England only, excluding London), and in Coseley.

1951 Outbreak

During 1951, 108 confirmed cases of diphtheria occurred in the whole area under review, of which 58 were in the Urban District of Coseley. Table II shows the ratio of notifications to confirmed cases and deaths.

Of the 34 unconfirmed notifications in Coseley, 12 (35.3%) had nasal or throat swabs positive for *C. diphtheriae* at some time and 22 (64.7%) never had a positive swab. Of the 44 unconfirmed notifications in the surrounding districts, 4 (9.1%) had positive swabs and 40 (90.9%) had not. These patients had initial signs and symptoms suspicious enough to prompt the action taken by their doctors, but the signs were transient, as no evidence of clinical diphtheria was found after admission to hospital. Those cases with early positive swabs may have been carriers, but this is not thought likely, as there was no previous history of diphtheria or chronic nasal discharge, nor were any positive swabs obtained subsequently. It is much more likely that they were, in fact, minimal clinical cases which rapidly overcame the disease after contracting it. They form an appreciable percentage of the unconfirmed notifications.

TABLE II.—*Diphtheria Cases and Deaths, 1951*

Area	1951 Census Population	Notifications	Confirmed Cases	Deaths
Coseley U.D. ..	34,414	92	58	1
* Surrounding districts	232,836	94	50	5
Total ..	267,250	186	108	6

* Bilston M.B., Darlaston U.D., Rowley Regis M.B., Sedgley U.D., Wednesbury M.B., Willenhall U.D., Tipton M.B.

Of the surrounding districts the one most affected in the outbreak was Bilston M.B., which borders on Coseley and had a population at the 1951 Census of 33,464. There were 18 cases with 3 deaths. Four cases were in one family and 15 were in schoolchildren. Reference is made below to the action taken in Bilston. In the remainder of the surrounding districts 32 sporadic cases occurred.

Seasonal Incidence.—In Coseley, cases occurred steadily throughout the year, but this was not so in the surrounding districts, where the outbreak did not gather momentum until the late summer, reaching a peak in November.

Age and Sex Incidence.—The age incidence of confirmed cases only is shown in Table III. Children of school age formed 65.5% of the total cases in Coseley and 65.7% of all cases.

The confirmed cases are classified according to age group and sex in Table IV. The sexes were attacked in approximately equal numbers in pre-school- and school-children.

TABLE III.—*Age Incidence of Confirmed Cases of Diphtheria, 1951*

	0–4 Years		5–14 Years		15 Years and Over		All Ages	
	No. of Cases	Rate*	No. of Cases	Rate*	No. of Cases	Rate*	No. of Cases	Rate†
Coseley U.D. ..	12 (20·7%)	3·86	38 (65·5%)	6·72	8 (13·8%)	0·32	58 (100%)	1·69
Surrounding districts	9 (18·0%)	0·43	33 (66·0%)	0·91	8 (16·0%)	0·05	50 (100%)	0·21
All cases ..	21 (19·5%)	0·87	71 (65·7%)	1·69	16 (14·8%)	0·08	108 (100%)	0·40

* Attack-rate per 1,000 related population (approximate).
† Attack rate per 1,000 related population on 1951 Census.

TABLE IV.—*Age and Sex of Confirmed Cases of Diphtheria, 1951*

	0–4 Years			5–14 Years			15 Years and Over			All Ages		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total
Coseley U.D.	7	5	12	20	18	38	4	4	8	31	27	58
Surrounding districts ..	4	5	9	17	16	33	—	8	8	21	29	50
All cases ..	11	10	21	37	34	71	4	12	16	52	56	108

Clinical Features

Of the 108 confirmed cases, 61 (56.5%) were classed as mild, 25 (23.1%) as of moderate severity, and 22 (20.4%) as severe, including the 6 fatal cases. In 74 the nose and/or throat swabs were positive for the gravis type of organism, but 34, although diagnosed clinically as diphtheria cases, did not have positive swabs. The exclusive occurrence of the gravis type of diphtheria has not resulted in a generally severe clinical form of the disease. The case fatality of 5.6% compares with 8.1% in the 11,492 gravis cases reviewed by McLeod (1943).

Of the 108 patients, 106 were admitted to hospital, the mean stay being 53 days; the longest stay was 152 days for a boy of 6 whose illness was of moderate severity but whose tonsils were removed for persistently positive swabs.

The complications were those commonly associated with gravis diphtheria. Of the 16 patients who were severely ill but recovered, 15 had paralyses, as did 8 of the 25 moderate cases and 3 of the 61 mild cases. One patient who died showed paralysis; the others did not live long enough to show it. Nine patients, including all the fatal cases, had bull-neck. Only three patients had a laryngeal membrane, and these were all mild cases; 27 had a pharyngeal, palato-pharyngeal, or nasopharyngeal membrane, and these included the 6 fatal cases and 13 of the 16 other severe cases.

Of the six patients who died five were children between the ages of 7 and 11 years, all of whom died within seven days of admission to hospital. The other was a male schoolteacher, aged 31, who died after 28 days in hospital. The cause of death in each case was myocarditis.

Spread of the Disease

In spite of the majority of cases being in schoolchildren there was little evidence that the infection was spread in school. The occurrence of cases was not affected by the school holidays, nor could a series of cases be found in the same school or class in circumstances suggesting transmission from one child to another by any of the classical and recognized methods, such as the sharing of pencils, contiguous position in class, and so on.

While in most cases there was little or no evidence to show how or from whom the infection was obtained, some of the confirmed cases were concerned in multiple infections in the same household. Nine families in Coseley between them had 23 individuals with positive swabs. Eighteen of these were later confirmed as having clinical diphtheria, this number being 31% of all confirmed cases in Coseley. The occurrence of the first case in each household was as difficult to explain as was the spread within the household easy. These first cases and the 69% of cases arising singly occurred sporadically and irregularly without traceable cause in the great majority of cases.

The location of the cases in Coseley, particularly in relation to the distribution of population, was most interesting. Coseley is not an isolated industrial town with a central business and shopping area, an inner industrial ring, and an outer suburban residential area in the usual way. It is rather a group of a dozen or so villages of varying size spaced throughout the 3,300 acres of the district, the villages being separated by stretches of waste and agricultural land interspersed with factories. During 1951, 59 (76.6%) of the total of 77 individuals found to have positive swabs lived in only five of these relatively sharply defined areas, the remaining areas either escaping completely or having only the odd scattered case. The cases were bunched in a striking manner. In one of these localities, the worst affected, there were 13 confirmed cases and 11 other persons with positive swabs living within an area of about 12 acres.

In the other four areas those with the infection were similarly clustered, though in smaller numbers. In spite of this, interrogation of contacts, neighbours, friends, etc., failed to show any connexion between the cases. Chronologically the cases in these areas did not link up, as they occurred often at widely spaced intervals of time. Inquiries failed to establish connexions between the cases except in one or two instances. It was unlikely, for example, that pre-school children would be in the habit of playing with children aged 12 years or more living near by. The weight of the evidence suggests that the infection was spread at home rather than at school, yet little specific evidence of home spread in individual cases was elicited except for those in the same family.

While these five areas are well defined, they have services common to other areas in Coseley and the surrounding districts. The same public transport, places of entertainment, main shopping centres, and so on are used by people of the affected and unaffected areas and of the surrounding districts. No explanation can be offered of why the cases should be so sharply confined for so many months to the affected areas.

The experience in previous years of the various areas in Coseley is of some interest. Records show that the incidence has been greatest in different areas at different times. Those suffering heavily ten years before escaped entirely in 1951, and vice versa. The irregular movement of the infection from one year to the next resembles that described by Grant (1951) during the years 1936–46 in Gateshead, and by Newsholme (1898) in his report on the 1888–96 epidemic of diphtheria in London.

The possibility that milk might be the vehicle of infection was investigated, but there was no evidence to support this.

The fact that the incidence was highest in schoolchildren led to a search for carriers in the schools and to an inquiry into the immunization state of the child population.

Search for Carriers in Schools

Between June 11 and 22 nose and throat swabs were taken from every child in eight school departments in Coseley. Five of these departments were those in which the greatest number of cases had occurred, and the other three, having only one case between them, were used as controls. The results are summarized in Table V.

Thus in school departments A to E, where the incidence of notified and confirmed cases of gravis diphtheria was 1.5%, a further 1% of the children were found to be harbouring *C. diphtheriae gravis* in the nose or throat, while in Departments F, G, and H, where the incidence of confirmed cases was 0.16%, no further children were found to be harbouring the organism. It must be emphasized that these figures are small and that they are based upon swabbing carried out on one occasion only.

The 15 children with positive swabs were free of symptoms, but nevertheless the evidence seems in favour of their being subclinical cases of diphtheria rather than carriers; none had any history of diphtheria or chronic nasal discharge, and their infection cleared up rapidly upon isolation in hospital; only five had any history at all of adequate immunization within the previous three years. If this is accepted, the investigation showed no evidence of a higher carrier rate in those schools with a number of cases of diphtheria than in those where none or only one case had occurred. As is mentioned above, there was an association in their home surroundings also between the children who were confirmed cases and those found to be harbouring the organism on swabbing, so that these bacteriological findings do not particularly indicate spread of the infection at school.

TABLE V.—*Results of Nose and Throat Swabs of Coseley Schoolchildren*

	School Departments with Highest Incidence of Diphtheria					
	A	B	C	D	E	All Departments
Confirmed cases of diphtheria January 1–June 11, 1951	9	4	3	3	2	21
No. of children on roll	449	371	155	183	242	1,400
No. with positive swab for gravis diphtheria in addition to confirmed cases	1	5	3	1	5	15
Incidence of confirmed cases	2·0%	1·1%	1·9%	1·6%	0·83%	1·5%
Incidence of additional positive swabs	0·24%	1·3%	1·9%	0·55%	2·1%	1·0%

	School Departments (Controls)			
	F	G	H	All Departments
Confirmed cases of diphtheria January 1–June 11, 1951	0	0	1	1
No. of children on roll	278	102	228	608
No. with positive swab for gravis diphtheria in addition to confirmed cases	0	0	0	0
Incidence of confirmed cases	Nil	Nil	0·44%	0·16%
Incidence of additional positive swabs	Nil	Nil	Nil	Nil

Immunization State

The percentage of the child population who had completed a course of immunization at any time before December 31, 1950, according to the annual returns, is shown in Table VI. It is seen that 73% of the school population of Coseley were shown in the return for 1950 as having been immunized.

This method of estimating the immunization state of the child population has, however, obvious disadvantages. It takes no account of the recency or otherwise of the immunization, nor, in the case of schoolchildren, whether they have had a reinforcement dose preceded by adequate primary immunization. It was thought that, in estimating whether or not a child could be regarded as probably adequately protected by immunization, stricter criteria were needed, and for the purpose of this investigation an admittedly arbitrary standard of complete immunization within the preceding three years was adopted. For all those children swabbed in the schools mentioned in Table V, a detailed survey of the immunization records was made and the result is shown in Table VII.

This result must be qualified by stating that the County Council's immunization records in their present form date only from April, 1949, when they were collated from the previous unstandardized records and a new system of supervision of immunization was introduced. It is probable that the percentage adequately protected, on the rather strict criteria set out above, was appreciably higher than 26.9%; this supposition is strengthened by the results of the inquiry made into the immunization state of those who were confirmed cases of diphtheria, in a number of whom a history of immunization was obtained from relatives or patient, although not entered in the records.

The criticism may also be made that estimation of the antitoxin content of the blood, or even the Schick test, would have been a better method of assessing the probable immunity or susceptibility of these schoolchildren than a scrutiny of the available records of their immunization. Unfortunately it was impracticable to carry out these tests for the 2,008 children.

The total school population of Coseley U.D. in June, 1951, was approximately 4,403, and, although the sample of 2,008 was not entirely unselected (especially as regards age and economic status), the results given above certainly indicated a much lower state of protection against diphtheria of the school population of Coseley than would appear from the official returns or would generally be regarded as necessary to prevent an outbreak of diphtheria.

Reference must here be made to the conclusion of the Tyneside and Dundee investigators (Hartley *et al.*, 1950) that a person inoculated as a child can expect to secure for himself early and adequate protection should he be exposed to infection in later life, because even in the absence of a reinforcing dose the infection itself serves as a secondary stimulus so that antitoxin is rapidly produced, and the disease is mild. Thomson (1951) also concludes, from statistics available to the Ministry of Health, that the prognosis for those who contract the disease, but who at some time have been immunized, is much better than that of those who have never had any such protection.

Nevertheless, the importance of the reinforcing dose of antigen in causing a rise in antitoxin titre, thus protecting the individual against *an attack* of diphtheria, and the community against an outbreak, remains unchallenged. It is possible that the present standard form of immunization return to the Ministry of Health may give an unduly optimistic impression, especially with regard to schoolchildren, and that further analysis of immunization records of local

TABLE VI.—*Percentage of Child Population Immunized Before 1951*

	Age Group			Age Group	
	0–4	5–14		0–4	5–14
Coseley	32	73	Tipton	24	96
Bilston	33	81	Rowley Regis	37	95
Wednesbury	47	89	Sedgley	51	93
Willenhall	42	86	Darlaston	26	79

TABLE VII.—*Immunization Record of Children Swabbed*

Presumably adequately protected:	
With complete primary course within previous 3 years	152
With complete primary course followed by a reinforcement dose, the latter within previous 3 years	388
Total	540
Unprotected or inadequately protected:	
No record of immunization	764
Primary course more than 3 years previously; no reinforcement dose	589
Record of incomplete primary course only	32
Record of "reinforcement" dose only	68
Complete primary course with reinforcement more than 3 years previously	15
Total	1,468
Proportion of 2,008 children investigated whose immunization records showed evidence of adequate protection within previous 3 years	26·9%

TABLE VIII.—*Immunization Records of Confirmed Cases*

Severity	Age (Years)	Presumably Adequately Protected*	Inadequately Protected†	No Record of Immunization
Mild	0–4	1 (3)	— (—)	10 (8)
	5–14	4 (6)	6 (22)	27 (9)
	15+	— (—)	— (6)	13 (7)
Moderate	0–4	— (2)	— (1)	7 (4)
	5–14	1 (1)	2 (6)	13 (9)
	15+	— (—)	— (—)	2 (2)
Severe	0–4	— (—)	1 (—)	2 (3)
	5–14	1 (1)	1 (5)	16 (12)
	15+	— (—)	— (—)	1 (1)
		7 (13)	10 (40)	91 (55)
		6·5% (12%)	9·2% (37·1%)	84·3% (50·9%)

In parentheses is shown the immunization state based upon the history obtained from relatives and (where possible) from the patient.

* Complete primary course within previous 3 years or complete primary course followed by a reinforcement dose—the latter within previous 3 years.

† Primary course more than 3 years previously—no reinforcement dose, record of incomplete primary course only, record of "reinforcement" dose only or complete primary course with reinforcement more than 3 years previously.

health authorities might show a less favourable state of affairs than is believed to exist. The immunization records of the 108 confirmed cases are shown in Table VIII.

Thus, although 49.1% of all the confirmed cases had some history of immunization, only 12% had been protected adequately within the preceding three years. Of the 22 severe cases, however, only 7 (31.8%) had any history of immunization at all, and of the six patients who died five had never been immunized, while the sixth, a girl of 8, had only a doubtful history of immunization in infancy. Two of the children who died had, however, received one dose of antigen—one about 24 days and the other about 11 days before the onset of the illness.

Of the 31 individuals whose swabs were positive (30 for gravis and 1 for intermedius diphtheria), although they were not clinically confirmed cases, 11 appeared never to have been immunized, while not more than seven were adequately protected.

Action Taken

By the end of September, 31 cases had occurred in Coseley schoolchildren, and it was also plain that the level of immunity of the child population was too low. A special letter was distributed through the teachers to the parents of each child attending the Coseley schools, urging the need for immunization and including a form of consent. Immunization was offered in this way for all the children, irrespective of their immunization history, and consent was obtained for 87%. A full primary course was given to each child, A.P.T. being used for all infants (aged 5–7), and T.A.F. for all secondary-school children (aged 11–15); the intermediate group (aged 8–10) were given A.P.T. or T.A.F. at the discretion of the medical officer performing the immunization. About 3,500 children were thus immunized; the operation began on October 22, and the great majority were completed by December 7.

In the meantime seven Bilston schoolchildren contracted the disease during November, and one died. A schoolmaster in a Bilston school who lived in Coseley also had diphtheria (and died later). A similar immunization campaign was therefore undertaken for the Bilston schoolchildren. Here 79% consents were obtained and about 4,000 children were given a primary course between December 10, 1951, and February 28, 1952, out of a school population of approximately 6,089, leaving a further 800 to be completed after that date.

Both at Coseley and at Bilston the proportion of consents obtained from parents was higher in the presence of the outbreak of diphtheria than had been customary. At the same time the ordinary measures to secure the immunization of pre-school children were intensified.

It was not expected that the special campaigns would produce enough immunity in Coseley and Bilston schoolchildren to control the outbreak of diphtheria until two to three months after their conclusion, but in fact the incidence fell markedly in Coseley at the end of 1951, and in Bilston in February, 1952, especially in schoolchildren. Whether the fall was wholly due to the immunization is uncertain.

From January 1 to November 3, 1952, 17 confirmed cases of gravis diphtheria occurred in Coseley, and 11 in the surrounding districts, but six of these were in Bilston in January and February, before the immunization campaign could have been effective.

Of the other 22 patients, 11 were schoolchildren and 6 pre-school children, but only five had ever been immunized. Of these five three were brothers and sisters who became ill within a few days of each other at the end of October, together with three other sibs, two of whom were unimmunized confirmed cases and the other a symptomless carrier or subclinical case.

Summary and Conclusions

A report is made on an outbreak of gravis diphtheria in Coseley and the surrounding districts in which 108 cases with six deaths occurred during 1951 in a population of 267,250 and a further 31 persons were found to be harbouring the organism.

In Coseley there had been for some years an incidence of diphtheria unusual in this country since immunization became general, and the change in the prevalent types of *C. diphtheriae* had been opposite to that in England and Wales as a whole—namely, from mitis to gravis and intermedius. The outbreak was provided with a fertile soil by the low level of immunity of the child population, and was not, so far as can be said, the result of the development of a strain of *C. diphtheriae gravis* more than usually capable of overcoming the immunity produced by the ordinary diphtheria antigens.

Long-term carriers appeared to play no part in the spread, and the large number of persons found to be harbouring the organism with slight or no symptoms were probably subclinical cases or transient carriers—that is, the result and not the cause of the outbreak.

The infection was probably spread mainly at home rather than at school, although most of the cases were in schoolchildren. No explanation can be offered of the remarkable grouping of confirmed cases and others found to be harbouring the germ in certain areas in Coseley.

In the two districts most affected the incidence fell immediately after mass immunization of the school population.

The outbreak emphasized the importance of a constant watch upon the proportion of children receiving reinforcement doses of diphtheria antigen, and showed that reliance upon the figures prepared for the annual immunization return may be misleading, especially where schoolchildren are concerned. It occurred in an area in every district of which at least 73% of the school population had completed a course of immunization at some previous time. Nevertheless, the outbreak provided further evidence for the belief that the risk of severe illness or death is reduced for those who have at any time been immunized. It also demonstrated the greater willingness of the public to accept immunization when they are confronted with an outbreak of diphtheria.

We gratefully acknowledge the facilities for the investigation afforded by Dr. G. Ramage, County Medical Officer of Health for Staffordshire. We wish to express our thanks to Dr. B. C. Haller, Medical Officer of Health, Bilston M.B., for information concerning diphtheria in Bilston; to Dr. R. N. Phease, Director of the Stafford Public Health Laboratory, for swabbing 2,008 Coseley schoolchildren and for collating information on the types of diphtheria organism found at the laboratory in the years 1946–50; and to Dr. C. Simpson Smith for kindly supplying clinical details of the hospital patients.

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The British Hospitals Contributory Schemes Association has published Part I of a directory of convalescent homes serving the provinces (England and Wales). All the 42 names included have been recommended by hospital contributory schemes affiliated to the association. The directory, which is in stencilled form, may be obtained from the association, Royal London House, Queen Charlotte Street, Bristol, 1, price 1s. 6d. H.R.H. the Duke of Edinburgh recently consented to bestow his patronage on the association.

PIGMENTED SCARS

BY

B. S. CRAWFORD, M.B., F.R.C.S.

Registrar, Plastic and Jaw Department, United Sheffield Hospitals

This communication is concerned with those scars, usually of the face, which follow injuries in which pigmented material becomes embedded in the skin and often in the subcutaneous tissues. Those which follow road accidents are the most common, and they are considered in some detail; reference is also made to pigmented scars following injury in coal-miners. Although scars are inevitable after such injuries, most of them would be inconspicuous, and some almost invisible, but for their contained pigment. It is not appreciated by many of those responsible for the initial treatment of these patients that the pigmentation of scars can be prevented by methods which do not require special experience for their application.

There are few references to the methods of preventing the pigmentation of scars, but short accounts are given by Matthews (1946) and Straith and Pilling (1947). In the American literature Iverson (1947) and Sheehan and Swanker (1950) refer to the treatment of established pigmented scars, but I have been unable to trace any work on this subject in the British literature.

Cases of injury in which pigmented material has been forced into the tissues can be divided into two groups—a large one in which the injuries are abrasive in type, and a small group in which the injuries follow an explosion.

Abrasive Injuries

Most of the cases in this group are the result of injury to exposed skin when the subject is flung forward along a road surface as the result of an accident. Motor-cyclists, cyclists, and pedestrians who are poorly protected—especially about the face—are most likely to sustain this type of injury. The skin is lacerated and abraded as it slides over the rough surface of the road, and loose particles of road grit become embedded in the wounds. Those parts of the face which are rendered prominent by the underlying bony skeleton—namely, the upper part of the nose, upper lip, chin, malar and supraorbital regions—usually sustain the severest damage, the lacerations running in various directions owing to the fact that the skin, which is stretched over the bony prominences, is split by impact with the irregular road surface. In these areas the lacerations usually penetrate as far as the subcutaneous fat and may reach the underlying bone, but in areas less firmly supported—for example, the cheek below the level of the malar prominence, and the neck—they take the form of multiple parallel abrasions of the skin which run in the direction in which the patient was travelling during the injury.

Immediately adjacent to these lacerations and abrasions there may be little or no evidence of damage to the skin, although foreign particles are embedded in it in large numbers. Lesions of the lower half of the nose, other than trivial ones, are uncommon, because this portion has a cartilaginous framework which allows it to be thrust aside at the moment of impact; this exposes the upper lip, which, no longer protected by the nose, is injured with unexpected frequency. The lower lip becomes everted as the head slides in a forward direction during the accident, exposing the buccal aspect to direct injury by the road surface, and in many cases the mucosa is split transversely just above the floor of the buccal sulcus. After a severe injury all the areas mentioned above may be damaged; in most cases, however, only one or two of them are found to be involved, but in practically all cases the lesions are confined to one side of the face.

Exposed skin surfaces other than those of the face—for example, the hands and knees—may also be affected; the knuckle regions of the hands are commonly involved, and in addition similar lesions of the anterior aspect of the knees may be seen in women and children.

In coal-miners lesions almost identical with those due to road accidents are seen as a result of coal falling from the "roof." Sometimes the face is directly damaged, but more often the back receives the force of the impact; the face is then injured if the miner is thrown forward on to it.

Explosive Injuries

In civilian practice pigment-contaminated wounds due to injury by high explosives are rare, and are most likely to be encountered as a result of accidents in industry.

In coal-mining, barriers of stone or coal are sometimes removed by shot-firing, in which a charge of T.N.T. or nitroglycerin is placed in a prepared hole, which is then filled or "stemmed" with a mixture of clay and sand. If the charge explodes before the worker takes cover the skin of exposed areas is tattooed by coal, shale, and stone fragments, with the addition of the materials used in "stemming." Identical injuries may follow the explosion of a compressed-air cylinder in a coal-mine.

Clinical Features of Pigmented Scars

The patients complain of conspicuous scars which excite unwelcome attention, particularly if they are on the face; those with pigmented scars on the upper lip, for example, complain of the frequency with which they are told that their nasal toilet is incomplete. The pigmented scars which follow injuries of the abrasive type are found in one or more of those areas which sustain damage in the way described, their depth and direction varying, like those of the original wounds, with the site of injury. Pigmented scars overlying bony prominences are almost invariably deep and run in various directions; scars in other situations are usually superficial, the pigmentation lying in parallel lines which are generally vertical in direction. The colour varies from light grey to black, depending on the concentration of pigment in the skin.

Multiple blue-black scars in exposed areas (scalp, back, and extremities) are extremely common in coal-miners, who rarely complain of them; indeed, they are usually proud of these marks of their trade. Those of the face which may follow explosive injuries, however, are most disfiguring (Fig. 1). They present a blotchy appearance, as most of the pigmented material lies in scattered pockets of deep damage.

During the first few months after injury many pigmented scars are raised, indurated, and erythematous, and it is remarkable that after this period the scars gradually become flat and supple, in spite of the fact that they still contain a great deal of foreign material.

Pathology

Examination of a wound or abrasion of the skin within a few hours of the injury will reveal an exudate of serous fluid which soon dries to form a surface coagulum. In the case of wounds or abrasions impregnated with pigmented foreign particles, the coagulum is found, on naked-eye and microscopical examination, to contain large numbers of foreign particles. These have also been found to be present in cases in which the surface had previously been freed of contaminants by swabbing and irrigation. It is therefore inferred that pigmented scars contain only those foreign particles which have remained embedded in spite of this natural attempt at extrusion.

A number of pigmented scars removed from a variety of cases were sectioned and examined by Dr. J. L. Edwards, who reported the presence of three types of foreign body: (1) doubly refractile material with sharp edges—possibly

FIG. 1 FIG. 2

FIG. 1.—Pigmented scars in a coal-miner resulting from a shot-firing accident.
FIG. 2.—The same patient as in Fig. 1, one year after treatment by the method described in the text.

silica; (2) black fragments which resemble carbon particles; and (3) scanty yellowish fragments, not anisotropic, which are possibly vegetable matter. The tissue reaction is a mild chronic inflammation without obvious giant-cell formation.

Chemical analysis of two typical samples of road grit taken from the outskirts of an industrial town show a high content of silica, tarry material, and carbon (see Table).

Chemical Analysis of Road Grit

	Sample A	Sample B
Siliceous grit	66·75%	56·10%
Tarry matter	1·50%	2·70%
Free carbon	3·73%	5·51%

The remainder consists almost entirely of calcium salts, of which the carbonate predominates. Samples A and B were collected three miles and two miles respectively from a town centre.

The results of these two methods of investigation suggest that the pigmentation of scars which follows road accidents is due to carbon particles and possibly also to tarry material. It seems probable that the sharp-edged particles of siliceous grit are forced into the tissues during the injury, carrying the pigmented materials with them. The high silica content of the foreign material may account for the early induration of some of these scars, which, however, become supple within six to twelve months of their infliction, although they remain pigmented. Rarely is the tissue reaction excessive, producing a granuloma in the form of a hard subcutaneous nodule, which on section shows a giant-celled foreign body reaction around particles of silica.

The pigmentation of scars seen in coal-miners is due to coal and possibly also to shale.

Prevention of Pigmentation

Absolute prevention is possible only by the use of masks or screens, and these might be usefully employed by those engaged in shot-firing. In practice, the pigmentation of scars is prevented by the removal of all pigmented foreign particles from wounds before healing occurs. Early treatment gives the best results, but in cases seen for the first time on the third or fourth day after injury the removal of foreign particles can still be carried out satisfactorily.

Local analgesia is recommended for the treatment of small lesions and also for extensive injuries in which the patient is regarded as unfit for general anaesthesia. Most cases are treated under general anaesthesia, and an intratracheal tube and a throat pack are inserted in all cases of extensive facial injury.

Operation

A good light is essential. The wounds are swabbed with 1% cetrimide to remove surface contaminants, and sterile towels are then draped in the usual manner. Areas in which abrasions have not penetrated deeper than the skin are treated as follows. The coagulum of dried serum which forms on the surface of the wounds within the first few hours of their infliction is removed with the sharp edge of a No. 11 blade, following which the point of the blade is used to tease the foreign particles out of the skin by scraping lightly with a to-and-fro movement. The knife is held at right-angles to the surface, which is put on the stretch. This method causes much less damage to the skin than would be expected, and I prefer it to scrubbing the wounds with a bristle brush, which is often employed. These areas of superficial damage are treated post-operatively by exposure, and the fresh coagulum which forms separates spontaneously in 7 to 14 days to leave a healed surface.

In areas in which the continuity of the skin has been broken the foreign particles are best removed by excision of the contaminated tissues (fat, muscle, etc.). Although pigmented particles at this depth do not cause visible pigmentation, they should nevertheless be removed as they encourage suppuration, and, in addition, the silica associated with them may be responsible for hypertrophy of the resultant scars. The amount of tissue excised is so small that the loss passes unnoticed both from the functional and from the cosmetic point of view. The removal of skin is undesirable and rarely necessary, especially on the face, where it has exceptional viability. Loose tags are excised, but the skin edges can often be freed of foreign particles by scraping with the knife point as described above. If this method fails a narrow strip of the affected skin edge is removed by paring with fine scissors. When all foreign particles have been removed, wounds of the deeper tissues are sutured, using a minimal quantity of fine catgut. The orbicularis oculi, for example, is often injured, and should be repaired; sutures may also be required to obliterate dead space. The operation is completed by closure of the skin by direct suture or, if there has been skin loss, by local flaps or free grafts. After operation areas of deep damage are covered by pressure dressings for four to five days.

If a thorough removal of foreign particles has been carried out the routine use of antibiotics is unnecessary, especially in cases of facial injury, in which infection is rare.

Treatment of Pigmented Scars

The use of cosmetics in an attempt to hide pigmented scars is unsatisfactory, but they may be tried in females if treatment has to be delayed. Surgical treatment is advised in practically all cases, and a variety of methods can be employed.

In the technique I use it is important to decide pre-operatively the depth to which pigment has penetrated in each area. *Superficial* pigmentation is usually spread diffusely over an area which has little or no bony support—for example, the cheek and the lower portion of the nose—scarring is slight or absent, and the colour is often light grey owing to the small amount of pigment present. *Deep* pigmentation, on the other hand, is found in localized areas overlying bony prominences, obvious scarring is always present, and the colour is dark and often black.

The treatment of superficial pigmented scars depends upon the fact that the epidermis and superficial layers of the dermis will regenerate if they are removed, leaving little or no evidence of permanent damage. Sheehan and Swanker (1950) advocate the use of sandpaper for the treatment of superficial scars, and I have found this method, which produces excellent cosmetic results, easy to apply. It is unnecessary to obtain the special boilable waterproof sandpaper which they employ, as ordinary sandpaper can be dry-sterilized in sealed glass jars placed in a hot-air oven at 160° C. for one hour.

In areas in which the pigmentation has penetrated as far as the deep layers of the dermis but not beyond the skin, Iverson (1947) removes the affected layers so far as is possible by sandpapering, relying upon the application of chemical coagulants to complete the removal. I have found this method difficult to control, and prefer to apply the one described by Sheehan and Swanker (1950), in which the affected skin is shaved off with a skin-grafting knife or a scalpel blade.

Anaesthesia.—Local analgesia can be used if the lesions are small, but most cases require general anaesthesia. In cases in which a large area of the face is treated, the use of hexamethonium compounds is of great value, as they not only reduce the blood loss but also provide a clearer field in which to work.

Operation.—If the pigmentation in a given area appears to be superficial, but the exact depth cannot be decided upon, the surface layers should be removed by sandpapering. If this is ineffective the remaining pigmented skin is then removed by shaving, using a skin-grafting knife, or a scalpel-blade if the area is small. In the treatment of pigmented scars which involve the deep layers of the dermis (Fig. 1) successive thin layers of skin are shaved off until a point is reached when the only remaining pigment consists of small areas of fine discrete black dots. At this stage all that is required is the removal of these areas by shaving with a small scalpel blade. In order to reduce to a minimum the amount of skin removed, these areas are picked up in turn between finger and thumb, or by means of a fine hook, and successive fine shavings cut from them until all pigment has been removed. In the event of small pockets of pigment having penetrated deeper than the skin, they are excised at the risk of causing a small amount of scarring, and the defects so caused are closed by suture, care being taken to arrange that their long axes lie parallel to the lines of Langer. Although a perfect cosmetic result is not obtained, the final appearance in suitable cases (Fig. 2) is better than that which follows the use of free grafts to replace the excised pigmented areas.

Many deep pigmented scars which involve the skin and subcutaneous tissues are linear, and can be treated satisfactorily by excision and suture. If after excision of a deep pigmented scar it is found that direct suture is impracticable, the defect is covered either by a local flap or by a free graft, as the case demands.

Summary

Pigmented scars are a common cause of disfigurement after injury. The pigmentation can be prevented by early and vigorous treatment of the initial wounds, and the attention of those concerned with the management of accident cases should be drawn to this fact. The treatment is relatively easy to carry out, in contrast with the treatment of established pigmented scars, which is often difficult.

I wish to thank Mr. W. Hynes for his advice and for permission to publish the cases mentioned in this article. I am also indebted to Dr. J. L. Edwards for the pathological investigations, to Mr. A. O. Jones for the analyses, and to Mr. J. Larway for the photographs.

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ANALYSIS OF 50 CASES OF PERSISTENT DUCTUS ARTERIOSUS

BY

F. STARER, L.R.C.P.&S.Ed.

(From the Thoracic Surgical Unit, Leicester)

The possibility of surgical cure of persistent ductus arteriosus was first suggested by Munro in 1907 (see Gross, 1939). Although some unsuccessful attempts had been made before 1939, it was not until that year that Gross successfully accomplished this. Since then several large series have been reported from the U.S.A., but so far there have been relatively few publications on the subject in this country.

Between October, 1947, and September, 1951, 53 patients were admitted to the Thoracic Surgical Unit, Leicester, for ligation of a persistent ductus arteriosus. Operation was performed in 51 instances. Of the remaining two, spontaneous obliteration of the ductus had occurred in a child aged 6 while she was awaiting admission to hospital. The second case was that of a boy aged 12 whose ductus became infected and as a result appeared to have become obliterated by fibrosis; this incidentally cured his infection. One patient who had the classical signs and symptoms of a persistent ductus arteriosus was found at operation to have an obliterated ductus, and an alternative diagnosis of a ruptured sinus of Valsalva was made. The following analysis is concerned with the remaining 50 patients on whom ligation was actually carried out.

Analysis of Cases

Incidence.—In this series there were 45 females and 5 males—a ratio of 9 : 1. This confirms the well-known preponderance of females in this condition, and in fact represents a higher proportion of females than is usual. Brown (1950) collected the figures of several series and obtained an incidence of 2.5 : 1. No selection in favour of females was carried out, and it is difficult to know why the preponderance in this sex was so much higher than usual. The average age at operation was 9 years; the oldest was 40 and the youngest 3 years old.

History.—The age of the parents was known in only 12 instances. In these the fathers' ages averaged 33 years and the mothers' ages averaged 31 years. There were no cases of rubella or other known significant disease during pregnancy, but two of the children were born prematurely. Three patients had a significant family history. In one case the mother had a persistent ductus arteriosus; in another a twin sister (identical twins) also had a persistent ductus arteriosus; and in a third a younger sister died as a baby of congenital heart disease. It is interesting to note, on the other hand, that one of the children with a persistent ductus arteriosus had an identical twin who was quite normal. The affected child was poorly developed compared with her twin, but made rapid progress after ligation of her ductus. In most of these patients the ductus was first diagnosed on routine examination, commonly when first entering school. In only four cases was attention drawn to the ductus by symptoms, although other cases developed symptoms after diagnosis.

Symptoms.—Nine patients complained of dyspnoea at the time of operation; of these, two were in failure and two were infected. Only the patients in failure showed cyanosis; they also had oedema of the legs and palpitation. Those who presented with infective endarteritis had fever, headache, chest pains, enlarged spleen, and in one case aphasia and ataxia. Peripheral manifestations of the end-

arteritis were conspicuously absent; there were no cases of peripheral emboli, with the possible exception of the patient who showed aphasia. Only three patients had red cells in the urine, but several showed evidence of pulmonary emboli. The rarity of peripheral emboli when infection of a ductus occurs is a result of the direction of the blood flow, which is from aorta to pulmonary artery—that is, from high to low pressure. Consequently, blood clot tends to be carried into the lungs. Peripheral emboli may, however, occur under two conditions: (1) when spread of the infection has occurred to the mitral and aortic valves; and (2) when there is reversal of the shunt as a result of pressure changes in the aorta and pulmonary artery. This occurs when congestive failure supervenes.

Blood Pressure.—As would be expected, a high pulse pressure was found (average 64 mm. Hg, highest 90 mm. Hg, lowest 25 mm. Hg). No correlation was found between pulse pressure and the size of the ductus. The exercise test (Bohn, 1938) was carried out in 11 instances only, and produced a diastolic fall in eight and a rise in two. In one case the response was variable. This suggests that, although the test is not infallible, it is a useful means of confirming the diagnosis. Again no clear correlation could be found between the response to exercise and the type of ductus.

Signs.—All the patients had the classical machinery murmur. One patient had been known to have a ductus murmur for many years; when the ductus became infected there were periods when the murmur could not be heard. This could be due to one of two causes—either the ductus was becoming blocked by vegetations (this seems to have happened in the boy previously mentioned) or it might have been due to equalization of pressures as the left ventricle began to fail. There would then be little flow of blood through the ductus. This seems the more likely explanation, since it was observed that shortly before operation the murmur again became difficult to hear, and during that time the patient was cyanosed, suggesting a reversal of the shunt. On the other hand, a machinery murmur was heard in the second patient who was in failure. Although the machinery murmur is a very constant sign in persistent ductus arteriosus, it may be absent in very young children and during cardiac failure; it disappears when the ductus becomes obliterated or blocked by blood clot or vegetations, and, of course, following ligation. On the other hand a machinery murmur may rarely be present in the absence of a persistent ductus arteriosus. It may be heard in unusual sites in a persistent truncus arteriosus or aneurysm of the sinus of Valsalva. A case in which such a murmur was heard is reported by Biörck and Crafoord (1947); it was due to an aneurysmal communication of an anomalous branch of the left coronary artery and a pulmonary artery. In 32 patients a thrill was felt.

X-ray Appearance.—Nineteen patients were thought to have had cardiac enlargement as judged from a simple postero-anterior film. Three of these had associated cardiac defects, leaving 16 cases of pure persistent ductus arteriosus with cardiac enlargement. Of these, five were infected and four probably infected. On the other hand, three infected cases showed no cardiac enlargement. This suggests that cardiac enlargement should make one suspect the presence of infection. Gross enlargement was present in both cases of failure; of these, the patient who was also infected presented the typical picture described by Gilchrist (1945), with a prominent pulmonary artery and patchy consolidation of the lung fields.

Incapacity.—Of the 50 cases of persistent ductus arteriosus, 33 were never incapacitated in any way. One was incapacitated by heart failure, one by palpitations, and nine when they became infected (of these, one developed congestive failure as a result of infection). One woman with an infected ductus had had a child a short time before the diagnosis was made. It is of importance to note that in addition six children had their activities unnecessarily curtailed by their parents. One child of 11, in particular, had never been allowed to go to school. It would seem that parental overanxiety is the second common incapacitating factor in persistent ductus arteriosus.

Congenital Abnormalities.—The following congenital abnormalities were found in association: one case each of spina bifida, left-sided vena cava and arachnoidactyly, interventricular septal defect, subaortic stenosis, narrowed aorta not amounting to coarctation, and possibly a second case of left superior vena cava.

Complications

Seven cases were with certainty infected, and five were probably infected. The following case is of interest in this connexion.

Case 1.—A woman of 25 had been known to have had a ductus arteriosus since childhood. In April, 1951, she began to complain of sweating, chills, and breathlessness. Blood culture produced a growth of *Streptococcus viridans*, and a diagnosis of infected persistent ductus arteriosus was made. Treatment with penicillin brought initial improvement, but she relapsed when that was stopped after six weeks. She was then treated with aureomycin without response. It was found that so long as she was given 600,000 units of procaine penicillin daily she would keep well, except for occasional chills and joint pains. There were no peripheral signs of the infection. Anxiety was occasioned by the intermittent disappearance of her murmur. She began to accumulate oedema and was intermittently cyanosed. It was decided to ligate her ductus in spite of the smouldering infection, and operation was carried out five months after the onset of infection. The ductus was large and friable, but ligation was carried out without any great difficulty. After operation the patient's condition gave rise to anxiety, as her oedema increased and she developed multiple ventricular extrasystoles. She was treated with digitalis and diuretics with steady improvement. For the first time in three months it was possible to stop penicillin without a recurrence of symptoms and elevation of her temperature.

Cardiac failure as the first manifestation is illustrated by the following case.

Case 2.—A woman aged 40 presented with congestive cardiac failure. She was not hypertensive, and gave no history of rheumatic fever. On examination there was a typical machinery murmur, and *x*-ray examination showed marked cardiac enlargement, a prominent pulmonary artery, and congestive changes at both lung bases. There was calcification in the aortic knuckle. At operation the ductus was found to be calcified, and it was tied with tape, as it was feared that a silk ligature would break it. After operation there was rapid improvement in her condition and she was able to lead an unrestricted life.

Operation

The postero-lateral approach was used in all cases. Ligation with heavy silk was carried out in most of them, two ligatures being used in two grooves. Where possible, a few drops of 50% glucose solution were injected between ligatures to promote fibrosis of the ductus. In no case was division attempted. In most instances no difficulty was experienced. In three cases bleeding occurred from the ductus; two of these were infected, and once there was considerable bleeding from a large pulmonary artery. Excessive oozing occurred in three cases. On every occasion bleeding was fairly easily controlled.

Controversy exists regarding the merits of simple ligation as compared with division of the ductus. As early as 1939 Gross stated his belief that division would be preferable, but at that time thought it would not be feasible. He points out that ligation in continuity of a vessel is against all accepted principles of vascular surgery. Shapiro (quoted by Potts *et al.*, 1949) collected 643 cases of persistent ductus arteriosus operated on by 46 surgeons; of these, 8.7% recurred. Wangensteen *et al.* (1949) report two recanalizations out of 16 ligations. In view of these figures many surgeons now prefer to divide and suture the ductus. That recanalization is not impossible even then is shown by a case of Crafoord's (1948). Ligation is still the operation carried out by many surgeons, including Blalock (1946). It is preferred in this unit, as it would appear to be a safer

procedure. So far there have been no recurrences among the 50 cases operated upon. Naturally the number of recurrences will depend on the criteria accepted in diagnosing such an event, and a minimal leak may produce marked signs. Hence the figures quoted above may exaggerate the incidence of recanalization following simple ligation. It should be noted that a systolic pulmonary murmur often persists for some time after ligation, presumably as a result of dilatation of the pulmonary artery.

Although on the whole no particular anxiety was felt during most operations, the dramatic and serious events in the following case make it worth recording.

Case 3.—The patient, a girl aged 13, had suffered no symptoms, though she was mentally rather backward. Operation was carried out under thiopentone, followed by nitrous oxide and oxygen and a procaine drip. Immediately the chest had been opened it was noticed that there was practically no bleeding. The heart was inspected. The auricles were seen to be contracting irregularly, while the ventricles were at a standstill. Cardiac massage was begun at once, followed by intracardiac adrenaline. The ventricles resumed beating immediately, and continued to do so strongly and regularly. It was estimated that they had been standing still for two to three minutes. It was decided to proceed with the operation, and this was carried out without further difficulty. After operation the patient was given cytochrome C, 2 pints (1.1 litres) of quadruple-strength plasma, and sodium succinate. She continued unconscious for two days in an attitude resembling decerebrate rigidity. A hopeless prognosis was given to her parents; nevertheless she regained consciousness and entered a period of restlessness lasting about ten days. Henceforth her mentality improved slowly, though it was many weeks before she could feed herself and had regained continence. Six months after operation she returned to school, though she has difficulty in coping. Nevertheless she appears to be improving.

An exactly similar case is described by Wangensteen *et al.* (1949). One must conclude that it is well worth while to persevere in the treatment of such cases, which in the early stages would appear to be utterly hopeless.

Post-operative Course

One boy aged 6 died two days after operation. He was a typical case of persistent ductus arteriosus, and operation was straightforward. On his way to the ward he was allowed to become cyanosed, and this was not discovered for some time. Although he eventually recovered consciousness he died of cerebral anoxaemia after two days. This death is directly attributable to a shortage of trained nursing staff. One patient had a mild wound infection which cleared rapidly. Four patients developed pleural effusions which cleared completely. One patient had a pulmonary infarct; this was one of the infected cases. Two patients required bronchoscopy for post-operative lung collapse, and one patient produced four or five tracheal casts.

Follow-up Period

This has been up to four years, and there have been no recurrences. The woman aged 40 who was in failure recovered completely—this being one of the few types of cardiac failure in which complete recovery is possible. The infected cases all recovered completely, irrespective of the use of antibiotics. In most cases, however, an attempt was made to cure the infection first by the use of large doses of penicillin. The children who were handicapped by the knowledge of heart disease have all returned to a normal life.

Summary and Conclusion

Fifty cases of ligation of persistent ductus arteriosus, with one death, are analysed. Ten physically handicapped patients made a complete recovery, and six who were held back by the knowledge of heart disease were allowed to return to normal life.

No certain knowledge is available to show how many of the asymptomatic cases, had they been left alone, would have gone on to obliteration of the ductus. It is well known that persistent ductus arteriosus is uncommon in the elderly, and this is sometimes taken as proof of the poor prognosis of the condition. On the other hand, it may mean that obliteration does occur more often at a later age than is at present recognized. Nevertheless, operation seems well justified in view of its low mortality as compared with the dangers of a persistent ductus—mainly subacute bacterial endarteritis and cardiac failure. In some cases the accelerated growth and development following operation are striking. For these reasons operation should not be too long delayed, and about 7 years probably represents a good age to operate.

My thanks are due to Mr. G. L. Cruickshank, who carried out the operations, for permission to publish this series.

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REDUCTION OF POST-OPERATIVE PAIN

BY

D. LINCOLN LEWIS, *M.C.*, M.Chir., F.R.C.S.

AND

W. A. L. THOMPSON, M.B., Ch.B.

(From the Royal Salop Infirmary)

The object of this communication is to present a simple way of diminishing post-operative pain in abdominal incisions. Briefly, analgesia is obtained by injecting procaine every three hours into the rectus sheath through polythene tubes for a period of three days. The method was first used by Blades and Ford (1950) in chest operations, and they suggested that it might prove successful in abdominal surgery. It was subsequently employed by Gerwig, Thompson, and Blades (1951) in 24 patients undergoing cholecystectomy. These writers came to the conclusion that it guaranteed satisfactory analgesia in upper paramedian incisions.

Pain is the chief factor preventing full respiratory excursions and adequate coughing after abdominal operations. Pain can be diminished by morphine, but morphine has an inhibitory effect on the cough reflex, and this may cause pulmonary complications sufficient to endanger a patient who has had an operation such as partial gastrectomy. Pooler (1949) found that pulmonary complications occurred in 19% of patients after upper abdominal operations. Using a spirometer, he found that there was a great diminution in vital capacity. He came to the conclusion that reflex muscle spasm was the chief cause of this reduction, and something more than the abolition of conscious pain was required. This could be accomplished only by interrupting the reflex arc on the afferent side.

Present Investigation

We were led to try the method of local infiltration with procaine, with a few modifications, after observing the reactions of a healthy young man who developed pulmonary collapse following a simple laparotomy through an upper paramedian incision. He had a great deal of pain in the

wound and needed five injections of morphine and pethidine during the first three post-operative days. He would not cough even with persistent encouragement. His temperature rose to 103° F. (39.4° C.) on the second day and remained at over 100° F. (37.8° C.) for three days. It was felt that this complication could have been avoided by the use of some method which reduced wound pain locally.

In this investigation polythene tubes were used in a consecutive series of 30 upper abdominal operations (see Table). The method adds less than 30 seconds to the operative time.

Summary of Cases

Case	Age	Operation	Post-operative Temperature
1	59	Polya type of gastrectomy	100° F. (37·8° C.) 1st and 2nd days
2	46	" " " "	99° F. (37·2° C.) 1st, 2nd, and 3rd days
3	48	" " " "	100° F. 1st and 2nd days
4	70	" " " "	100° F. 1st day
5	57	Billroth I gastrectomy	Normal
6	64	Polya type of gastrectomy	99° F. 2nd day
7	48	" " " "	99° F. 1st and 2nd days
8	47	Billroth I gastrectomy	101·5° F. (38·6° C.) 2nd day, 100° F. 6th and 7th days
9	51	Polya type of gastrectomy	100° F. 1st day, 99° F. 2nd day
10	44	" " " "	99·5° F. (37·5° C.) 2nd and 4th days
11	42	Billroth I gastrectomy	99·5° F. 1st and 3rd days
12	54	" " "	99° F. 1st, 2nd, and 3rd days
13	34	Polya type of gastrectomy	100° F. 1st day
14	50	Billroth I gastrectomy	99·5° F. 1st day, 99° F. 2nd day
15	40	" " "	99° F. 1st and 4th days
16	37	Polya type of gastrectomy	100° F. 1st day, 99° F. 2nd day
17	49	" " " "	Normal
18	42	" " " "	99° F. 1st day, 99·5° F. 2nd day
19	50	Billroth I gastrectomy	100° F. 1st day, 99·5° F. 2nd day
20	51	Polya type of gastrectomy	Normal
21	52	Billroth I gastrectomy	99·5° F. 3rd day, 99° F. 4th day
22	31	Polya type of gastrectomy	Normal
23	54	" " " "	99° F. 1st day, 100° F. 2nd day
24	56	Billroth I gastrectomy	100° F. 1st and 2nd days
25	78	" " "	100° F. 1st day, 99° F. 2nd and 3rd days
26	55	Gastro-enterostomy	99·5° F. 2nd day
27	44	Billroth I gastrectomy	99° F. 2nd and 3rd days
28	40	" " "	99·5° F. 3rd day
29	52	Polya type of gastrectomy	99° F. 1st day
30	54	Billroth I gastrectomy	Normal

All the cases had considerable relief from pain a few minutes after the injections were given. This in itself should make it a valuable addition to post-operative treatment, since a sense of well-being improves morale. Patients were able to carry out their breathing exercises unhampered by pain, movement in bed was facilitated, and ambulation was made more comfortable. Another point of interest was that some patients found that the passage of urine and flatus was much easier after the injections of procaine. There was no delay in healing or any evidence of wound infection. It is obvious that great care should be taken not to introduce infection at the time of injection.

It was found, however, that many patients did not sleep during the first night, though pain was relieved. They did not complain of pain, but remained wide awake because cerebration was active. To combat this sleeplessness, an injection of soluble phenobarbitone, 3 gr. (0.2 g.), and pethidine, 100 mg., was given on the first night. In anxious patients this was repeated on the second night. The procaine injections were used only for the first three days after operation, as after this time wound pain was not severe enough to call for continuation of the treatment. A degree of euphoria was noted in some cases, possibly due to a central effect of procaine.

The method was also found to be successful in midline incisions, the tubes being placed between the peritoneum and the linea alba.

Anatomy

The rectus sheath is formed in its upper three-quarters by the aponeurosis of the internal oblique muscle, which splits at the lateral border of the rectus muscle into an anterior and a posterior layer. These layers fuse with each other and with those of the other side at the linea alba. The aponeurosis of the external oblique muscle fuses with this anterior layer and the transversus muscle with the posterior layer. In the lower quarter all three aponeurotic layers pass in front of the rectus muscle, leaving behind it only the fascia transversalis and the peritoneum.

The nerve supply of the rectus muscle, its sheath, and the subjacent peritoneum is derived segmentally from the lower intercostal nerves. T.7 supplies the upper part, T.10 the level of the umbilicus, and L.1 the lower part above the pubis. The terminal part of a typical lower intercostal nerve enters the posterior aspect of the rectus sheath near its lateral border. It supplies branches to the sheath and to the subjacent peritoneum. It then passes forwards, through the rectus muscle which it supplies, and terminates in the overlying skin.

Technique

After closure of the peritoneum a No. 16 B.W.G. needle is inserted through the skin 4 cm. lateral to the lower third of a paramedian incision, and continued obliquely upwards and inwards, passing through the anterior rectus sheath and the rectus muscle. Along the bore of this needle a size 1 polythene cannula is introduced into the space between the posterior rectus sheath and the rectus muscle. The needle is withdrawn and the polythene tube pulled upwards towards the costal margin. It is most important to be sure that this tube is as high up in the sheath as possible. Failure to ensure this will result in the patient's complaining of pain over the seventh and eighth costal cartilages. The pain is probably due to bruising of the cartilages by retraction at the time of operation.

A second tube is introduced into the upper third of the rectus sheath in the same way and passed downwards towards the lower end of the sheath. This method of placing the tubes lessens the chance of accidental removal before the end of three days. Further fixation of the tubes is obtained with elastic adhesive bandage in the form of a modified watershed dressing after closure of the wound.

Before the patient leaves the theatre 4 ml. of 2% procaine is injected into each tube. A further 3–5 ml. is injected every three hours into each tube for the next three days. The amount injected depends on the thickness of the abdominal wall. If only 2 ml. is injected the period of analgesia is very short. Penicillin, 300,000 units every four hours, is given the night before operation and continued for five days.

Conclusions

Procaine injected through polythene tubes into upper abdominal incisions satisfactorily controls post-operative pain.

The necessity for post-operative narcotics is greatly diminished.

Breathing and coughing are facilitated, with consequent diminution in pulmonary morbidity.

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The staffing of many small homes for old people which are being opened throughout the country is an acute problem, and in an attempt to meet this need the National Old People's Welfare Committee has initiated a training course for matrons and assistant matrons. The fourth of these courses, which are supported by the Ministry of Health, begins in October; it will last for four months and comprise theoretical teaching and practical training in the geriatrics units of London hospitals and in old people's homes. Local education authorities are encouraged to assist students from their areas with grants towards the cost of tuition. Further information about these courses may be obtained from the National Old People's Welfare Committee, 26, Bedford Square, London, W.C.1.

A "NEW" Rh ANTIBODY, ANTI-f

BY

R. E. ROSENFIELD, M.D.

P. VOGEL, M.D.

NATALIE GIBBEL, A.B.

Mount Sinai Hospital, New York, N.Y., and Bureau of Laboratories, Department of Health, New York, N.Y.

RUTH SANGER, Ph.D.

AND

R. R. RACE, Ph.D., M.R.C.S., F.R.S.

Medical Research Council, Blood Group Research Unit, the Lister Institute, Chelsea Bridge Road, London, S.W.1

A "new" Rh antibody, which we propose to call anti-f, has been found in the serum of a man, Mr. Cl., aged 30, who suffers from haemophilia.

Since childhood Mr. Cl. has received about 35 transfusions of blood, the last of which, in December, 1951, was followed by a shaking chill. He was seen by us, for the first time, in March, 1952,* when three blood-group antibodies were found in his serum—anti-B, anti-K, and anti-S. In addition there was at least one other unidentified antibody. In the hope of clarifying the reactions of this antibody 0.25 ml. of O, NsNs, cdE/cde, kk blood was injected on two occasions; following this, the presence of anti-N was disclosed and, in addition, the antibody anti-f, which is the main reason for this publication.

The blood groups of Mr. Cl. are: A_1, MsMs, P+, CDe/cDE, Lu(a−), K−, Le(a+b−), Fy(a+), Jk(a+b+).

The serum of Mr. Cl. can be absorbed free of the other antibodies, leaving anti-f alone. This absorbed serum has been used to test the blood of 276 unrelated white people and 114 of their relatives. From the results it is clear that the antigen recognized by anti-f is part of the Rh complex of antigens; it is also clear that the antigen is not associated with any other of the known blood-group antigens, with sex, or with the ability to taste phenylthiocarbamide.

Properties

In brief, the antibody reacts with a product of the chromosomes cde and cDe, which may consequently be distinguished by the addition of f. We have been able to classify all the important chromosomes save the rare $cD^{u}e$ (which we expect to have f).

If the absence of f is indicated by the letter F the chromosomes are:

cdef, cDef.

CDeF, cDEF, $C^{w}DeF$, CdeF, cdEF, $CD^{u}eF$, $cD^{u}EF$, CDEF, $CD^{u}EF$, $C^{w}deF$, and CdEF.

These are the *usual* Caucasian chromosomes. For reasons which will be given in a later communication, we expect certain less common combinations to exist—namely, cDeF, cdeF, CDef, and cDEf. We have found a sample of blood giving the reactions expected of cDeF/cdef and one giving the reactions expected of cdeF/cdef. If the genes are arranged in a linear order on the chromosome then the order DCEF fits best with the observed facts.

If anti-F exists, as we presume it does, it will be difficult to identify with the test cells commonly available: it will give the reactions of a mixture of anti-C and anti-E, and, furthermore, it may be combined also with anti-D.

*Referred by the Hemophilia Foundation, Inc.

Anti-f agglutinates red cells suspended in albumin, and the results can be confirmed by absorption tests. The reaction of homozygous, ff, cells is stronger than that of heterozygous, Ff, cells. The antiglobulin test is not particularly useful with this example of this antibody.

Anti-f does not promise to be of any great practical importance in routine Rh blood-group work. Certainly it splits off CDE/cde and CDE/cDe from CDe/cDE, CDe/cdE, and Cde/cDE; it also separates CdE/cde from Cde/cdE. But these are hardly day-to-day problems. There is evidence that anti-f may be present in some anti-e and anti-c sera, and so these sera are laid open to investigation from this angle.

From a theoretical point of view anti-f is obviously of the first importance and must be taken into account in any thought about the Rh groups. Many interpretations of this new antibody have been considered, but the reactions can be most simply and conservatively explained by the postulation of a fourth allelomorphic pair of Rh antigens, f and F.

A detailed account of the serological and genetical work on anti-f will be published soon, together with acknowledgment to many people who have helped us by collecting samples of blood of rare Rh genotypes.

THREE CASES OF SUPPURATION DUE TO FUSIFORMIS INFECTION

BY

W. M. R. HENDERSON, M.D.

Pathologist, Pembury Hospital, Tunbridge Wells, Kent

A number of non-sporing, non-motile, anaerobic bacilli have been isolated by different workers from necrotic lesions in man and animals. They represent an ill-defined group of organisms classified at the moment as the genus *Fusiformis* (Topley, Wilson, and Miles, 1948). The term "necrobacillosis" has been given to the disease they cause in man.

These organisms have been demonstrated in the normal flora of the mouth, intestines, and genito-urinary tract by Beveridge (1934) and others, and in a variety of human pathological lesions, including ulcerative colitis (Dack, Dragstedt, and Heinz, 1936), in osteomyelitis and mastoiditis (Chandler and Breaks, 1941), in infected wounds (Forbes and Goligher, 1944), in post-abortive fever (Jones, 1944), in puerperal fever (Harris and Brown, 1927), and in appendicitis (Veillon and Zuber, quoted by Topley *et al.*, 1948). These organisms have also been isolated from various necrotic conditions in animals, such as calf diphtheria and labial necrosis of rabbits. A fuller description of these organisms is given by Beveridge (1934), Lemierre (1936), and Schwabacher and Mitchison (1947).

Organisms of the *Fusiformis* group were isolated from the following cases of peritonitis (two cases) and ischio-rectal abscess (one case), and the characteristics of the organisms were substantially the same in all.

Case Reports

Case 1.—A married woman aged 45 was admitted to hospital on March 14, 1950, complaining of pain and tenderness in the right groin for the past eight days. On examination the abdomen was distended and shifting dullness was present. A large ill-defined mass was felt in the right loin and the overlying skin was red and oedematous. Laparotomy was performed next day and general peritonitis was

found with many adhesions. Gentle exploration of the upper right abdominal quadrant liberated a gush of foul-smelling pus, and 2 pints (1.1 litres) was removed by suction, a drain was inserted, and the abdomen was closed. A provisional diagnosis of appendix abscess was made at this time. A course of penicillin, 250,000 units twice a day, and streptomycin, 0.5 g. once a day, was started. In spite of this her temperature did not settle and a further operation was performed on March 23. At this a further 2 pints (1.1 litres) of pus was evacuated through a right subcostal incision, presumably coming from a subphrenic abscess. The patient slowly improved after this, although foul-smelling pus continued to be discharged from her wound for several days. The streptomycin was discontinued after nine days and the penicillin after two weeks, when a total of 6,250,000 units had been given. The patient made a slow but satisfactory recovery, and was discharged a few weeks later.

Case 2.—A man aged 64 came to the out-patients' department complaining of a painful lump on his buttock. On examination an ischio-rectal abscess was discovered. This was incised and about 4 oz. (114 ml.) of foul-smelling pus was evacuated. A drain was inserted, an injection of 1 ml. of "prolopen" was given, and the patient was sent home to rest. A further injection of prolopen was given next day, and the dressing was changed. Two days later he was feeling well and comfortable, and his abscess was discharging through the incision. A week later the wound was healed and the patient was completely cured.

Case 3.—A man aged 43 complained of sudden onset of pain in the lower abdomen. On examination he was pyrexial and there was generalized abdominal rigidity with tenderness in the right iliac fossa. A diagnosis of perforated abdominal viscus was made, and a laparotomy was performed the same day. Free pus was found in the peritoneal cavity, and the appendix was acutely inflamed and had perforated. The appendix was removed and a suitable drain inserted. Penicillin, 500,000 units a day, was given for seven days (a total of 3,900,000 units). Eleven days after admission he began to have rigors and a mass could be felt in the right loin. A second operation was performed, at which ½ pint (285 ml.) of foul-smelling pus was released under pressure from the right paracolic gutter. Two drainage tubes were put in, and a course of chloramphenicol was begun, 8.5 g. being given in five days. The patient made an uneventful recovery.

Bacteriology

In all three cases foul-smelling dirty-brown pus was obtained from the abscesses. Films stained by Gram's method showed pus ++, necrotic debris, and some small Gram-negative bacilli. In addition, in Case 2 some Gram-positive cocci and in Case 3 both Gram-positive cocci and large Gram-negative bacilli were also seen. The material was inoculated on to blood-agar plates and incubated aerobically and anaerobically.

The aerobic plates in Case 1 were sterile, in Case 2 they grew a few colonies of *Staph. saprophyticus* and *Bact. coli*, and in Case 3 *Bact. coli* only. After 24 hours' incubation the anaerobic plates in all cases showed some very small pin-point colonies resembling those of *Haemophilus influenzae*. After 48 hours the colonies measured 0.5–1 mm. in diameter, were smooth and convex, and were slightly opaque like drops of milky water. Stained films showed them to be composed of slender pleomorphic Gram-negative cocco-bacilli, some the size of *H. influenzae* and others as large as coliforms. There were also a few slender filamentous forms. A small zone of haemolysis was now apparent surrounding the colonies. The organisms were subcultured on to blood agar, plain nutrient agar, and into Robertson's meat broth and incubated aerobically and anaerobically. All aerobic plates remained sterile, but the organism grew satisfactorily on blood agar and plain agar under anaerobic conditions, and it also grew in Robertson's broth, from which it was again subcultured on to blood agar and grown anaerobically. At no time was the organism grown under aerobic conditions. The addition of a few drops of laked horse cells (to supply the X factor) or streaking the plate with *Staph. pyogenes* (to supply the Y factor) did not enable the organism to grow aerobically, but the growth on the anaerobic plates appeared to be improved by their addition, and "satellitism" around the staphylococcal colonies occurred.

In Case 3 an anaerobic streptococcus was grown as well as the fusiformis. The association of anaerobic streptococci with these organisms has already been quoted by Lemierre (1936). The organisms were kept going quite easily by subculturing every two or three days on to fresh blood-agar plates. Acid but no gas was produced in lactose, glucose, maltose, and saccharose, though not in dulcite or mannite. Two or three days' incubation in an anaerobic jar was required to produce a satisfactory growth in the sugars. The addition of serum to the sugar media did not appear to be necessary. Indole was produced by Case 3 but not by the other two. Gelatin was not liquefied by any of the organisms, and the reaction in milk was neutral. The organism from Case 3 was found to be sensitive to penicillin, streptomycin, and chloramphenicol; the others were not tested.

Broth cultures of the organisms from Cases 1 and 2 were inoculated subcutaneously into guinea-pigs with no apparent ill effect. The animals were killed four weeks later and no abnormality was discovered at the post-mortem examination. Unfortunately no rabbits were available at this time.

Discussion

The organisms from these three cases had very similar cultural and biochemical characteristics, which, so far as they went, also agreed with the descriptions by Schwabacher and Mitchison (1947) for two strains of the genus *Fusiformis* and by Topley *et al.* (1948) for *Fusiformis fragilis*. The organism from Case 3 differed from the others by producing indole, but Chandler and Breaks (1941), Forbes and Goligher (1944), and Owen and Spink (1948) all described indole production in their cases.

There is no doubt that there must be many strains in this group, as various individuals have reported different characteristics, but it is thought that the organisms described in this paper can reasonably be included in the genus *Fusiformis*—the main characteristics of the group being that they are non-sporing, non-motile, anaerobic Gram-negative cocco-bacilli which show a variable amount of pleomorphism and filamentous forms. The material from which they are originally obtained is usually foul-smelling pus. Colonial and morphological appearances resemble the *Haemophilus* group, but their ability to grow without X and Y factors, and their dependence on strict anaerobic conditions, exclude them from this group.

In dealing with material from the female genital tract it is important not to confuse fusiformis organisms with morphologically similar Gram-negative cocco-bacilli, which can often be grown from the normal vagina. These latter organisms are not true anaerobes and will grow aerobically as long as X and Y factors are present, but will not grow on plain agar. Moreover, the colonies are smaller and do not show the "milky water" appearance of fusiformis. As they can be found in the flora of the normal vagina of healthy adults and young girls, they are not regarded as pathogenic, and their dependence on X and Y factors for growth suggests that they may be members of the *Haemophilus* group, possibly related to *H. ducreyi*.

The three cases of necrobacillosis described in this paper all recovered, and the one organism tested was found to be sensitive to penicillin, streptomycin, and chloramphenicol. It therefore seems that with modern antibiotics, and surgical drainage where indicated, the prognosis in these cases is good.

Summary

Three cases of suppuration due to infection by fusiformis organisms are described. All made satisfactory recoveries.

The morphological and cultural characteristics of the organism are described, and are compared with those reported by other workers.

A morphologically similar organism found in the normal vagina, which must not be mistaken for fusiformis, is briefly mentioned.

With suitable antibiotic treatment, and surgical drainage where indicated, the prognosis in infection with these organisms is regarded as good.

I wish to thank both Dr. J. L. Pinniger, of St. Thomas's Hospital, London, in whose laboratory this work was done, and Dr. Mary Barber, of the Department of Bacteriology, St. Thomas's Hospital Medical School, for their helpful criticism and advice.

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EXPERIMENT TO DETERMINE IF A PROGUANIL-RESISTANT STRAIN OF P. FALCIPARUM WOULD RESPOND TO LARGE DOSES OF PYRIMETHAMINE

BY

S. AVERY JONES, M.R.C.S., L.R.C.P., D.P.H. D.T.M.&H.

(From the Division of Insect-borne Diseases, Medical Research Laboratory, Nairobi)

This experiment was undertaken to find out if a proguanil-resistant strain of malaria also showed partial or absolute resistance to pyrimethamine (" daraprim "). I was both subject and experimenter. By the co-operation of Dr. G. I. Robertson, of the I.C.I. laboratory, Nairobi, I received 10 bites by five mosquitoes (*A. gambiae*) infected with a proguanil-resistant strain of malaria parasite imported from the Tampin area in Malaya.

The biting took place on August 21, 1952. All mosquitoes showed sporozoites on dissection. Parasites appeared in the blood on September 1 (Day No. 1) (see Table).

Course of the Infection

Day No.	Maximum Parasitaemia	Ring/ Leucocyte Ratio	Treatment	Time of Treatment
1	38/50 leucocytes	0·7:1	50 mg. pyrimethamine	Noon
2	53/50 ,,	1:1	50 ,, ,,	,,
3	94/50 ,,	2:1	100 ,, ,,	,,
			100 ,, ,,	2 p.m.
			50 ,, ,,	10 ,,
4	625/50 ,,	12:1	10 gr. quinine i.v., 7 tab. chloroquine in divided doses	1 ,,
5	763/50 ,,	15:1	10 gr. quinine i.v. and 10 gr. by mouth, 6 tab. chloroquine in divided doses	1 ,,
6	58/50 ,,	1:1	4 tab. chloroquine and 20 gr. quinine in divided doses	

On the third and fourth days the white blood cell counts were 4,100 and 4,500 per c.mm. respectively. After the sixth day recovery was rapid, and I was able to leave hospital on the tenth day feeling fit. At no time was toxaemia profound, and mental clarity was retained throughout, though headache became very severe on the fourth day.

Discussion

I had not previously had malaria, so immunity played no part in the infection. The experiment proved that a strain of malaria resistant to proguanil can show absolute resistance to pyrimethamine. This is hardly surprising when it is realized that pyrimethamine resulted from research on the antimalarial properties of diaminopyrimidines undertaken because these compounds showed a structural analogy with proguanil and similarities of microbiological behaviour. It is probable that both drugs act upon the same enzyme system of the malaria parasite.

It is evident that medical policy in Kenya has been wise, in that the African population has not been subjected to treatment with proguanil on a large scale. Because of dispensing difficulties in Reserves this might have been given in doses small enough to allow the widespread rise of resistant strains. The same applies, in theory, to pyrimethamine, though the drug is effective in such small doses that this danger seems unlikely to occur. The sale of 5 mg. tablets for prophylaxis would be dangerous, as adult Africans would use them for treatment, with the certainty of underdosage. Perhaps only tablets of not less than 25 mg. should be allowed for sale. These are readily divisible for treating infants, and, as the drug has a very low toxicity, there seems little to fear from overdosage. Generally speaking, it is probable that the majority of people taking pyrimethamine will do so in doses that, though harmless, are far more than actually required to eradicate infection. The fact that the drug is tasteless and cheap should ensure this.

In a recent paper Wilson and Edeson (1953), as a result of work in Malaya, report no difference in response to pyrimethamine between unselected strains of malaria and those resistant to proguanil. East African strains of malaria parasites are extremely sensitive to pyrimethamine, though recently a case of subtertian malaria which did not respond to pyrimethamine has been encountered, the resistance of the infecting parasite being confirmed by subinoculation. It would be a tragedy if other resistant strains were imported. The presence of men of the King's African Rifles in Malaya creates a hazard, and it is hoped that special care will be taken that none return to East Africa with the gametocytes of Malayan strains of malaria in the blood.

I thank the Director of Medical Services, Kenya, for permission to publish this paper and Dr. B. P. Harris for undertaking treatment at the conclusion of the experiment, when intervention became necessary; thanks are also due to the senior parasitologist, Dr. R. B. Heisch, who watched the parasite rate when I was unable to do so, and to Dr. G. I. Robertson for the great help and interest shown by him in the experiment. The nursing skill and attention were beyond praise.

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This year the number of students applying for admission to American medical schools has again declined, according to a survey by the director of studies for the Association of American Medical Colleges. 3,150 fewer students applied this year than in 1951–2, 7,600 less than three years ago. Of the 16,763 persons applying last autumn only 7,778 were accepted. The survey also shows that the average pre-medical student applies to three or four medical schools, and that the geographical distribution of students is uneven, half the candidates coming from only seven States. One cautious student applied to 45 medical schools and was accepted by one.

Medical Memoranda

Persistent Ductus Arteriosus and Pregnancy

The following case is reported because of the current interest in congenital heart disease and on account of the rarity of a second confinement in a woman with persistent ductus arteriosus.

CASE REPORT

A woman aged 31, who withstood one previous confinement surprisingly well, and who had given birth to a healthy full-term infant in June, 1948, after a normal labour lasting 11 hours 40 minutes, was referred to hospital in March, 1951.

There was no history of rheumatic fever, chorea, or recurrent sore throats. She did not suffer from dyspnoea and had never noticed any oedema of the ankles. She had become pregnant for the second time, and the expected date of confinement was in June, 1951. On physical examination there was no clinical evidence of cardiac enlargement; the maximal impulse, which was normal in character, was situated in the fifth intercostal space, just inside the mid-clavicular line. A thrill and a loud clanging murmur were audible to the left of the manubrium. The murmur was maximal at the end of systole and continued through the second sound into diastole. The blood pressure was 125/70. The electrocardiogram was within normal limits. A skiagram of the chest revealed slight left ventricular enlargement and dilatation of the pulmonary artery. Pregnancy pursued its usual course, a normal confinement occurred in June, and the puerperium was uneventful.

COMMENT

Congenital heart disease comprises about 1% of all organic heart disease, so that it is a rare finding in pregnant women. Donovan (1936) expresses the opinion that congenital lesions constitute a contraindication to pregnancy. Most authorities entirely disagree with this opinion. In 1905 Pouliot stated that marriage was contraindicated in congenital heart disease only in the presence of cyanosis, and in 1912 Couderc concluded that if the condition was compatible with adult life the prognosis depended less upon the form of the lesion than upon the state of compensation, the size of the heart, the degree of cyanosis and polycythaemia, parity, and the advent of complications, especially tuberculosis and endocarditis.

Mendelson and Pardee (1941) review a series of 20 cases of congenital heart disease admitted to the New York Lying-in Hospital over a period of nine years. The total number of obstetrical patients in this period was approximately 31,000. In their series there were two cases of persistent ductus arteriosus, the average age being 24, and the average parity 0.5. There was no dyspnoea, cyanosis, polycythaemia, or any cardiac difficulty during pregnancy, labour, or the puerperium. Including the series of Couderc (1912) and Jensen (1938) there are 31 other reported cases of persistent ductus arteriosus complicating pregnancy. Jensen found the average age to be 27.2 and the average parity 2.2. There are six recorded deaths, only two of which can be attributed to the lesion—one patient died of congestive failure at five months' gestation (Von Schulcz, 1928) and the other died of congestive failure following caesarean section at term. There is no mention of any cardiac difficulty during pregnancy, labour, or the puerperium in the other cases.

In persistent ductus arteriosus the danger of a veno-arterial shunt developing during labour or the puerperium has been stressed in the literature. Alarming symptoms may unexpectedly develop immediately after delivery. The symptoms are dyspnoea and tachycardia without venous congestion. Carr and Hamilton (1933) suggest that these symptoms are due to a sudden fall in peripheral resistance following emptying of the uterus, and state that they are more apt to occur after caesarean section than after normal delivery. Certain precautions should be taken to avoid this possibility. Arterial blood pressure should be maintained by avoiding traumatic procedures and post-partum haemorrhage, or by promptly instituting appropriate measures in the event of such occurrences. Judicious use of forceps will obviate undue bearing-down pains, with resulting increased pressure in the pulmonary circuit. Particular attention should be paid to the avoidance of infection. Binding the limbs and abdomen after delivery has also been recommended.

My thanks are due to Dr. M. W. Bailie, who referred the patient to hospital. He conducted the second confinement and provided the details of her first pregnancy.

R. J. KERNOHAN, M.D., M.R.C.P., D.P.H., D.C.H.,
Physician, Mid-Antrim Hospital Group.

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Aberrant Branch of the Splenic Artery

In the course of dissection of museum specimens at Guntur, Madras State, the following variation has been noted. From the splenic artery a fairly large branch is seen to enter the spleen near the medial end (see Diagram). This is in addition to the usual branches that enter the spleen near the hilum. This branch is given off from the splenic artery before the left gastro-epiploic.

It is unusual to encounter branches from the splenic artery entering the spleen except at its hilum. Though it

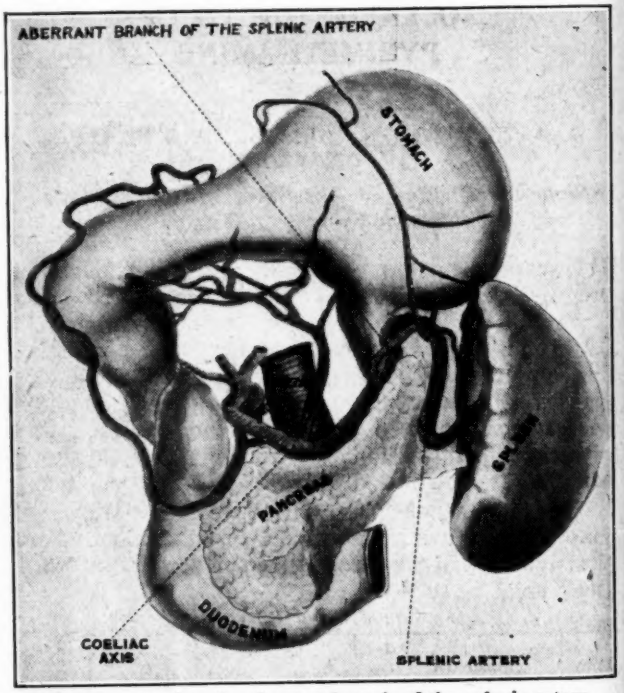

Diagram showing the aberrant branch of the splenic artery.

is a rare type of anomaly, this finding is described, as it has to be borne in mind by surgeons when performing a splenectomy. This arterial branch has to be separately ligated from the splenic artery, as this is given off proximal to the left gastro-epiploic artery. Failure to ligate arteries like this, when present, may account for some of the haemorrhages that result from splenectomy.

My thanks are due to the Principal of Guntur Medical College for the specimen.

V. SITARAMA RAO, M.B., B.S., M.Sc.,
Associate Professor of Embryology and Histology, Stanley Medical College, Madras.

Reviews

SCIENTIFIC BASIS OF MEDICINE

Lectures on the Scientific Basis of Medicine. Volume I. 1951–2. British Postgraduate Medical Federation. (Pp. 396; illustrated. £1 10s.) London: The Athlone Press. 1953.

This is described as the first of a series of annual volumes to be based on the series of lectures under this title which are arranged each winter by the British Postgraduate Medical Federation. Of the 39 lectures delivered during the winter of 1951–2, 18 are included in this first annual volume. The range of topics is wide, and it is not possible to summarize them in a few words. Most of the articles are transcripts of the lectures and run to 6,000–8,000 words. Two of them, however, have been expanded to over 20,000 words —"Studies of Normal and Pathological Physiology of the Kidney," by Van Slyke, and "Growth of the Human at the Time of Adolescence," by J. M. Tanner—and must therefore be regarded as reviews rather than lectures.

In previous book reviews I have expressed doubts about the value of collecting series of lectures into annual volumes unless they are of the nature of a symposium. The proper place for lectures on the scientific basis of medicine is in the weekly journals, despite recent suggestions that many members of our profession are interested only in reading a strictly practical journal for general practitioners. Leaving this question on one side, I believe that most doctors who have preserved the habit of reading would enjoy each and any of the 18 lectures printed in this volume, whatever branch of medicine they are pursuing, and the British Postgraduate Medical Federation is to be congratulated on having stimulated the production of these interesting lectures.

L. J. WITTS.

B.C.G. VACCINATION

B.C.G. Vaccination. Studies by the WHO Tuberculosis Research Office, Copenhagen. Report prepared under the direction of Lydia B. Edwards, M.D., and Carroll E. Palmer, M.D., Ph.D., with the assistance of Knut Magnus. Monograph Series, No. 12. (Pp. 307. 15s., $3, French francs 960, or Swiss francs 12.) Geneva: World Health Organization.

This monograph consists of a series of reports on work carried out by the World Health Organization's Tuberculosis Research Office at Copenhagen. The substance of many of the reports has already been published in British and American journals. The present volume, however, contains not only 150 pages of descriptive text but also a further 150 pages of appendices setting out the original observations in tabular form.

The chief aim of the inquiry was to study the numerous variables that affect vaccination with B.C.G. For this purpose the quantitative response of children to tuberculin was used as the main tool. Observations were made on a total of over 40,000 schoolchildren, most of them in Denmark, but some in Egypt, India, and Mexico. Instead of taking an arbitrary figure, such as 6 mm. of induration and over, as a positive reaction, the authors measured the transverse diameter of the reactions and plotted them as histograms. In this way surprising differences were revealed between the behaviour of unvaccinated children in different countries. In Denmark, for example, a high proportion of all children were insensitive to the intradermal injection of 10 T.U. In Egypt and Mexico, on the other hand, some of the children were insensitive or practically so and others reacted strongly, thus giving a bimodal histogram. An increase of dose to 100 T.U. had little effect on the non-reactors in Denmark, but converted many of the non-reactors in Egypt to weak reactors. The authors therefore recognize a high-grade type of sensitivity characterized by a strong reaction to a small dose of tuberculin, and a low-grade type characterized by a weak reaction to a small dose and a stronger reaction to a large dose. They bring evidence to suggest that the high-grade type of sensitivity is alone indicative of specific infection with the tubercle bacillus.

Other studies lead to the conclusion that there is no simple relationship between the severity of the local reaction after B.C.G. vaccination and the strength of the subsequent allergic response; that B.C.G. vaccine retains its full potency for at least four weeks when stored at 2–4° C., but falls off rapidly at temperatures over 30° C.; that sunlight has a most damaging effect on the vaccine, five minutes' exposure to Egyptian sunshine destroying 99% of the organisms; and that the degree of allergy produced by a given batch of vaccine depends to some extent on the proportions of living and dead bacilli present.

This work, it need hardly be said, is of absorbing interest to the immunologist, and has important practical applications to the attempted control of tuberculosis by vaccination. It is pioneer work carried out by visionaries in the international field, raising more problems than it has solved, and emphasizing once more the danger of assuming that epidemiological conclusions reached in one country are necessarily valid for other countries. The World Health Organization is to be congratulated on its wisdom in fostering this inquiry, and Dr. Carroll Palmer with his associates for their imagination and skill in undertaking a task of such magnitude.

G. S. WILSON.

THE WHITE PLAGUE

The White Plague: Tuberculosis, Man, and Society. By René and Jean Dubos. (Pp. 277. 15s.) London: Victor Gollancz. 1953.

This book is written for laymen as well as for scientists. The reconciling of the language of medicine with presentation to the non-medical reader is always a difficult task. The writer is apt to be too technical and prosy for the layman, or too simple and trite for the pundit. The authors here have skilfully avoided either extreme, and the result is a book of equal interest to both classes of readers.

Part I is devoted to the "White Plague" in the greater part of the nineteenth century, when it was rife, favoured by overcrowding, treated in overheated, ill-ventilated rooms, believed not to be contagious, and the cause was unknown. It often assumed epidemic proportions when introduced into schools, convents, barracks, and among primitive races. To adorn the tale, accounts are given of famous sufferers from the disease—for instance, Keats, Shelley, Paganini, Chopin, and the Brontës. With regard to the Brontës, the usual view is adopted that the Reverend Patrick Brontë was a chronic consumptive and infected his children. It seems more probable that the tuberculosis which destroyed one by one all the members of that gifted family was contracted primarily at Cowan Bridge School, the "Lowood" which Charlotte pilloried in *Jane Eyre*. Two sisters, Maria and Elizabeth, were infected there and, presumably, Charlotte and Emily also. Maria and Elizabeth died after being brought home, and they or Emily transmitted the infection to their brother Branwell and sister Anne. Tuberculosis was endemic in the school. The authors consider there may be some basis for the statement that consumption fosters and nourishes genius, but, as Dr. Andrew Morland has pointed out, creative artists and writers, engrossed in their work and often exposed to privation in their early years, are a likely prey to the tubercle bacillus.

Part II is on the causes, Part III on the prevention and cure of tuberculosis, and Part IV on tuberculosis and society. The book thus ranges over a wide field in the discussion of a complex subject. The authors seem sceptical about therapeutic and surgical treatment and put more faith in public health measures, common sense, and individual and social conscience than in B.C.G. and chemotherapy. Prevention

has achieved much in lowering the incidence and mortality of tuberculosis, and it is highly important in Britain that the treatment of tuberculosis under the National Health Service shall be closely co-ordinated with the preventive work of the local authorities.

Epidemiologists are unlikely to agree with the contention on p. 185 that a study of mortality curves over 150 years shows that tuberculosis began to decrease before any specific measures had been taken against the disease. Reliable figures of the mortality from all forms of tuberculosis in England and Wales first became available since the decennium 1851–60, and do show a marked decline. Since 1848, however, environmental hygiene has greatly improved, especially for the poor. There has been a higher standard of living, more institutional segregation of the highly infective patient, cessation of indiscriminate expectoration, and, as a consequence of these things, less exposure of the public to massive infection. Furthermore, the direct attack on tuberculosis must have exerted a beneficial effect. Yet tuberculosis is still a killing disease, and this book should help to stimulate further endeavour, especially as regards co-operation of the public in preventive measures.

ARTHUR S. MACNALTY.

BRITISH PSYCHOLOGY TO-DAY

Current Trends in British Psychology. Edited by Professor C. A. Mace, M.A., D.Litt., and Professor P. E. Vernon, M.A., D.Sc., Ph.D. (Pp. 262. 15s.) London: Methuen and Co. 1953.

In 1951 the psychology section of the British Association for the Advancement of Science decided in the Festival year to devote their annual meeting to presenting a survey of the work of psychologists in this country. This book contains 20 papers by senior representatives of the different fields of work written for the intelligent layman or the scientist of another discipline, and is therefore ideal for the suspicious medical reader who is doubtful of the credentials of this relatively youthful science.

The first ten papers are devoted to the application of psychology to practical problems. Industrial psychology, arising from the inquiry into the health of munition workers in the first world war, is now concerned with such subjects as working conditions, incentives, and joint consultation, while clinical psychology, which began with the testing of backward children, has now become a valuable aid to psychiatric diagnosis and treatment. Vocational guidance and educational selection are seen recovering from the enthusiasm for test procedures which invaded the Army and the educational system in the war years and after. It is interesting to learn that the interview, the general knowledge test, and even the examination paper are returning to favour, and that the Civil Service Selection Board has moved from the house at Stoke d'Abernon where candidates were subjected to ordeal by house-party.

The second ten papers are concerned with the fundamental concepts and methods of psychology, and particular interest attaches to the work of Professor O. L. Zangwill on the application of psychology to brain function in neurological disease. The studies of defects at the higher levels of integration carried out at the National Hospital, Queen Square, offer the hope of partially quantifying the neurological examination and of extending the work of Goldstein to the problems created by hemispherectomy and other ablations now surgically feasible.

These short papers are for the most part free of technical jargon and give the medical reader the opportunity to judge for himself which workers are contributing something to knowledge or to human welfare and which are suspect of producing a verbal soufflé rather than something more nourishing. On the whole this picture of British psychology shows that its place is established and that its feet are on the ground.

ALEXANDER KENNEDY.

X-RAY SIEVE THERAPY

X-ray Sieve Therapy in Cancer: A Connective Tissue Problem. By Benjamin Jolles, M.D., D.M.R. Foreword by Professor Sidney Russ, C.B.E., D.Sc., F.Inst.P. (Pp. 192; 51 illustrations. £1 5s.) London: H. K. Lewis and Co. 1953.

This work bears the stamp of individuality. The author has devoted most of his professional career to radiotherapy, and throughout his radiotherapeutic work has focused his interest on the connective tissue in its relationship to tumours and to radiotherapy. With some justification he deplores the apparent view of many of his colleagues, including cancer research workers, that the malignant cell is all-important, and he considers that the tissues in which they grow are neglected. He tries first to show the nature of the connective tissue from a discussion of a great deal of literature, emphasizing its highly organized, sensitive, and specific features. The impression made on me was that the connective tissue is important and complex, but the significance of many of the experimental and morphological facts quoted is still obscure. In discussing the importance of the connective tissue in its relationship to cancer he gives the reader increasingly more insight, but it is when he begins to discuss his own work on skin reactions and the development of the "sieve" or "chequer board" type of treatment field that he develops the authority which, even though one might criticize, most impresses the reader. His account of the importance of the periphery of a treated area or volume is original, well done, and of the highest importance. The use of the sieve is pioneer work in Britain, although parallel work has been done in other countries with less scientific basis. The criticisms I would make of this part are that he should have considered the differences between the chequer board and the sieve in which irradiated areas are not contiguous. He should also have discussed the significance of the very much larger doses apparently tolerated through a sieve of this type than any radiotherapist of experience has any right to expect; although such doses have been given in the U.S.A., and, following that experience, in Britain, though more cautiously.

The book is well documented, well printed, and well illustrated, and is to be commended, even though it has shortcomings, for its thought-provoking viewpoint. It should prove of interest to biologists and research workers as well as to those engaged clinically in cancer work.

FRANK ELLIS.

RADIODIAGNOSIS

Lehrbuch der Röntgendiagnostik. By H. R. Schinz *et al.* Part 8: Innere Organe. Fifth edition. (Pp. 454; 559 figures. M. 96.) Stuttgart: Georg Thieme. 1952.

This volume completes the new edition of the greatest Swiss work on radiodiagnosis, and it maintains the very high standard set by the earlier volumes. The authors discuss the radiography of all the abdominal organs and describe in elaborate detail the precise technique required in each individual case. In every instance we are offered the results of vast experience and of superb technical achievement, so admirably presented as to be of real practical value.

The illustrations throughout are of a very high order, both in execution and in production, and they are worthy of close study quite apart from the text. A special feature of the volume is the attention devoted to normal anatomy, and it is indeed a revelation to learn of the importance of anatomy as revealed by *x*-ray examination. Of special beauty are the illustrations of the gall-bladder and gall-stones, and of the genito-urinary system.

We are glad to hear that an edition in English will soon be brought out. It should have a wide appeal to all who are interested in the study of the human body in both health and disease.

HENRY SOUTTAR.

BRITISH MEDICAL JOURNAL
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THE EXTRAORDINARY GENERAL MEETING

The Extraordinary General Meeting to take place on May 5 at B.M.A. House is being held on the signed requisition of more than a hundred members of the Association. The requisitionists have put forward for consideration a resolution[1] which "requires the Council forthwith to approach the Minister of Health with proposals for the better protection (financial and otherwise) of the small-list doctor and of the doctor newly seeking entry into practice." They request that the implementation of the Working Party's scheme should be postponed until new proposals have been considered. The requisitionists are clearly dissatisfied with the present scheme, believing that the small-list doctors are being adversely affected, thus reviving the objections that were voiced about ten months ago. The requisitionists have a right to use the constitutional machinery of the Association to bring to the fore, even at this late date, their doubts about the distribution of the Danckwerts award. It is odd to criticize this as undemocratic, as an attempt by a minority to overthrow the wishes of the majority. It is surely essential to democracy that the minority voice should be heard; and, if it fails to convince the majority, then, properly, the majority will have its way. But surely the proper mechanism for this purpose would have been a special Representative Meeting requisitioned by the aggrieved through their Divisions, for the Representative Body is the final court of appeal and the arbiter of policy. It is unrealistic to propose that the Working Party's report should not be implemented, for its implementation has already been carried out. It is hoped, therefore, that the Extraordinary General Meeting will adopt Lord Horder's amendment[2] that this part of the requisitionists' resolution should be deleted. The meeting will then be able to debate the proposition that the small-list doctor and the new entrant to practice may not be receiving a fair deal.

It is as well to recall that in June and July last year the Special Conference of Local Medical Committees and the Representative Body accepted all the Working Party's recommendations for the distribution of money to general practitioners in the N.H.S., and accepted them with enthusiasm. In a letter to this journal in August last year Mr. Hilary Marquand[3] threw doubts on the scheme and considered it did not adequately improve the lot of the young and poorer-paid doctors. It appeared that he and the discontented wanted to load the capitation fee for the first thousand of a doctor's list. But in 1951 Mr. Marquand's own department, in its plans for a new distribution of the pool, referred to "improving the position of practitioners with lists of the order of 1,000 to 2,500." The Working Party's loading was, and is, on the thousand persons on a list after the first 500, giving a capitation fee of 27s. for numbers 501 to 1,500 on a list. It was suggested in these columns[4] that, as the average number of patients per doctor in England and Wales was about 2,200, it could be argued that the loading should be on the second thousand of a list. With the loading now in force, the initial practice allowance, and the notional list, it is logically difficult to see how the young and the new entrant should be hard hit. And, as we observed subsequently[5]: "A sound practice is not static, and to rob the Peter of the good established practice to subsidize the Paul of the unestablished practice would be to deprive general practice and its future practitioners of much healthy enterprise." The young man and the new entrant to general practice now have to put up with much less hardship than did their elders when they were young. It is good that it is so. But it would also be good if there were wider recognition of this fact.

It should, too, be recognized that provision was made for cases of hardship that might arise, as they must arise in any scheme of distribution however perfect—and who has ever yet devised a scheme that would satisfy everyone? The G.M.S. Committee has already set up an *ad hoc* committee of the medical members of the Working Party, of the Assistants and Young Practitioners Subcommittee, of the Medical Practitioners Union, and of the Amending Acts Committee of the B.M.A. to consider allocating a proportion of "the final settlement moneys for the purpose of remedying any obvious defects in the distribution scheme." In the terms of the rider to the Working Party's report,[5] such possible defects relate to "certain groups of practitioners who under the terms of reference of the Working Party might have expected to have benefited [but] have in fact not done so." In its recent report[6] the G.M.S. Committee observes that "its preliminary work was hampered by lack of reliable information as to the extent of the problem."

[1] See *British Medical Journal Supplement*, March 21, p. 76.
[2] Ibid., April 25, p. 152.
[3] Ibid., 1952, 2, 93.
[4] *British Medical Journal*, 1952, 2, 327.
[5] *British Medical Journal Supplement*, 1952, 2, 141.
[6] See *Supplement*, April 4, p. 99.

It argues that there is no case for altering the scheme to give additional help, for example, to the small-list doctors who are, or may become, junior partners, or to those eligible for the initial practice allowances. It admits that "there may remain a proportion of small-list practitioners devoting their whole professional time and ability to the running and the building-up of their practices for whom modifications may need to be sought."

What is now needed is the ascertainment of the number of doctors so affected. The full Working Party has already met, and has decided how best to obtain this necessary information. The number of hard cases cannot be large, but, however small, everything must and will be done to see that justice is done to them. This will best be accomplished if the Extraordinary General Meeting next Tuesday afternoon tackles the problem in a sober fashion with the aim of getting things done rather than of giving expression to grievances, some of which may turn out to be imaginary.

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis, sometimes called Pick's disease, is perhaps badly named, since the thickened pericardium does not constrict the heart but restricts the action of the cardiac muscle. Surgical decompression is the only effective treatment. Although not a common disease, it presents a typical picture. Early diagnosis can prevent chronic invalidism by allowing operative treatment before irreversible cirrhotic changes have occurred in the liver. Evans and Jackson[1] have recently reviewed 30 cases treated by operation in England, and Chambliss and others[2] 61 cases so treated in America. Their conclusions are similar. The disease is four times more common in men than in women, and most often seen in the fourth decade. Dyspnoea on exertion is the commonest symptom, typically disappearing at the moment of halting; it is unusual at rest. Swelling of the abdomen is often the symptom which leads the patient to seek advice; swelling of the ankles is almost as frequent, but usually occurs later. Fatigue may be marked. The onset is usually gradual, except when the disease follows acute pericarditis. Many of the physical signs resemble those of right heart failure, but bear a different emphasis. All patients with constrictive pericarditis have raised venous pressure, shown by distension of the veins of the neck and elsewhere, and all have an enlarged liver, which is firm and smooth but not tender. Pulsation of the engorged veins is a useful sign. The pulse is small, never slow, and seldom paradoxical, and the blood pressure low; about one-third of the patients have auricular fibrillation. Cyanosis may be seen; it is an unfavourable sign. Ascites or oedema is usually present, often both, the former generally more conspicuous, and paracentesis is often necessary. Pleural effusions may also occur. Features unlike those of heart failure are that the apex beat is seldom displaced and often difficult to palpate; significant murmurs are unusual, but an adventitious diastolic sound is often present, either a third heart sound or a split second sound. Further investigation assists diagnosis. The most informative radiographic sign is calcification, but this is absent in at least one-third of the patients. When present it is usually most conspicuous behind the heart or on the left border; the left anterior oblique view often demonstrates a convincing crescent. The cardiac silhouette is normal or somewhat enlarged in size, sometimes altered in shape to triangular or globular; the right border is prominent, partly from a raised diaphragm, and the superior vena cava may appear distended; there may be pleural effusion or thickening. On screening, diminished or altered pulsation is usually seen. The electrocardiogram will confirm an arrhythmia. The curve is often of low voltage, the T-wave usually low or inverted, and the P-wave often notched or broad. The circulation time is increased and the cardiac output diminished. Liver biopsy shows congestive cirrhosis with central fibrosis, which, if severe, suggests a poor prognosis after operation. If oedema is present the serum proteins are reduced.

Differential diagnosis must be made from valvular heart disease by the findings described, especially the relatively high venous pressure compared with the moderate dyspnoea and the small quiet heart without murmurs. Conditions to be considered include cirrhosis of the liver, in which the venous pressure is normal even when ascites and oedema are present; polyserositis, an inflammatory lesion involving more than one body cavity, of acute onset with fever, usually tuberculous in origin (if the pericardium is involved, constrictive pericarditis may follow, so that the effusions are perpetuated); and malignant ascites due to multiple metastases.

It is likely that constrictive pericarditis is usually of tuberculous origin. (Sound evidence has been brought forward by Andrews, Pickering, and Sellors[3] that there are other forms of chronic adherent pericarditis which do not give the usual clinical picture.) Sometimes tubercle bacilli can be cultured from operative specimens; many cases have progressed from acute

[1] *Brit. Heart J.*, 1952, **14**, 53.
[2] *Circulation*, 1951, **4**, 816.
[3] *Quart. J. Med.*, 1948, **17**, 291.
[4] *Arch. Surg.*, 1950, **61**, 266.

pericarditis known to be tuberculous, which, as it heals, restricts the heart; occasionally miliary dissemination has followed operation; other patients have had active tuberculosis elsewhere. The pathological findings in these patients are no different from those who present no direct evidence of tuberculosis, and in all cases it is unusual to find specific features on histological examination, which shows chronic inflammation with much fibrosis and few cells. The disease never follows rheumatic fever, but may occasionally be a sequel to acute non-specific pericarditis and rarely to trauma. It has been suggested that it is often due to the rupture of a caseous tuberculous mediastinal gland into the pericardial sac. Grossly, the pericardium is dense, fibrous, and thickened; both layers are affected and are adherent to the heart, which is encased and compressed; calcification is common and caseation occasionally present. The scar is seldom uniform but may involve any part of the heart, often invading the myocardium, which may even contain cold abscesses. Sometimes the scar is most marked in the atrio-ventricular groove.

The main effect of the constriction is reduction of cardiac output, both filling and ejection being limited, and this can be corrected only by removal of the encasing scar. In most cases it is the scar over the ventricles which is responsible for the disability. As fluid in the pericardium tends to gravitate to the back, the scar is often thickest over the posterior and inferior part of the heart, involving especially the left ventricle. A left-sided approach is therefore the most generally used, with either an anterior or more usually an extensive lateral thoracotomy, passing across the pleural cavity, which may itself be obliterated by adhesions. The relative immobility of the encased heart is striking; the surgeon should not be satisfied until normal action of the heart muscle is restored, and to allow this both parietal and visceral layers must be stripped. It is usually possible to do this by blunt dissection, but sometimes invasion of the myocardium makes it difficult. As much as possible of the heart is freed, avoiding only the region of the coronary vessels; their exact identification may be impossible, since they are often embedded in scar. Arrhythmias or cardiac arrest may occur, but are less likely if pauses are made in the dissection. Haemorrhage can usually be controlled by sutures or by replacing a small flap of the thickened pericardium.

In general the ideal time for operation is as soon as there is evidence of cardiac compression. In cases of insidious onset this will be indicated by the symptoms and signs mentioned, especially the raised venous pressure. In cases of recent acute pericarditis Evans and Jackson advise operating as soon as there is evidence of fluid retention in the body. Holman[4] also advises early operation and claims good results, although it was formerly considered that operation is dangerous until the disease is completely quiescent. If the patient has tuberculosis elsewhere, operation should be delayed. The operation is never an emergency, and the patient should be prepared by freeing him so far as possible from excess fluid, which may be evident as oedema or effusions, by restricting salt and fluid intake, by mercurial diuretics, and by aspiration. Many patients improve immediately after operation; in others improvement may be gradual or follow a delay, sometimes of many months. A second operation may be indicated, possibly using a right-sided approach to clear this side of the heart. To complete the decompression at one stage some surgeons use a midline incision, dividing the sternum completely either vertically or horizontally and spreading it widely to give access to the front and both sides of the heart.

Of Evans and Jackson's 30 patients, 18 have been relieved of symptoms for at least five years, and 5 others are improved. Of the 61 patients of Chambliss and others, 38 had excellent results, and 6 others were improved. Of about 500 cases reviewed in the literature and summarized by these authors, satisfactory results have been obtained in nearly 65%. Even in patients completely relieved of symptoms, the venous pressure often remains high, and residual calcification can be seen on a radiograph. A hospital mortality rate of about 15% is still to be expected; but without treatment, although the course may extend over years, natural cure does not occur, the symptoms are severely disabling, and in the end usually fatal.

ANTICHOLINESTERASES

There is a large and diverse group of chemical compounds showing the property of inhibiting those enzymes in the body which hydrolyse the esters of choline. They have gained the generic title of "anticholinesterase." This ugly name includes compounds developed for an ugly purpose, such as the newer war gases produced by the Germans during the last war. Other anticholinesterases more familiar to our readers include eserine and neostigmine and di-isopropyl fluorophosphonate (D.F.P.) used in clinical medicine, and organophosphorus compounds used as insecticides.

Probably the most important of the choline esters in the body is acetylcholine, on whose transitory presence at vital points depends the proper functioning of our brain, nerves, muscles, and glands. By its persistence, however, acetylcholine will undo all the good effects achieved by its passing, hence the importance of cholinesterase to ensure that it does not linger too long upon the scene. Neostigmine has been used successfully for

many years to treat myasthenia gravis, though we are still in the dark about the exact nature of this disease. Such new organo-phosphorus compounds as tetraethyl pyrophosphate and octamethyl pyrophosphoramide have been tried on a limited scale for this purpose but are so toxic that errors in dosage may have serious consequences. D.F.P. has been used to stimulate peristalsis in paralytic ileus and to contract the pupil in glaucoma.

The ever-growing knowledge about the toxic properties of the new organo-phosphorus anticholinesterases confirms the classical work of Loewi, Dale, and others, who first discovered the importance of acetylcholine and its attendant hydrolysing enzymes. In their work much use was made of the older inhibitor eserine. But a closer study of the action of the new and more toxic compounds has suggested new problems about the role of acetylcholine and cholinesterase. The scale of interest in these problems was reflected in an audience of 200 that attended a two-day symposium organized recently by the British Pharmacological Society and the Society of Chemical Industry. There were a dozen major papers and twice as many shorter contributions, as well as expert introductions and summaries of the four sessions. The interest of the symposium was not centred on medical problems but rather on the physiological and biochemical processes that are disturbed by the anticholinesterases. The action of the highly toxic war gases was described in detail by workers from Porton. This provided a welcome lifting on the ban of secrecy so long applied to work of this kind. The contribution gave an excellent illustration of how defence research can advance general scientific knowledge.

A number of papers posed new problems, though sometimes in a manner difficult to follow. There were two outstandingly clear papers on the use of these compounds as tools in research. One described a study on the nervous control of renal function. The other analysed the mechanism by which enzymes become inhibited. This may well lead to more knowledge of how enzymes work. The unexpected side-effects of some of these compounds which result in serious neurological lesions in both man and some experimental animals aroused considerable interest. The clinical picture of poisoning and the nervous lesions are the same as those known for many years to follow poisoning by tri-ortho-cresyl-phosphate (T.O.C.P.), itself an organo-phosphorus compound. A hypothesis that T.O.C.P. owed its action to its power to inhibit for long periods the cholinesterase associated with the white matter of the central nervous system has suffered the fate of the majority of hypotheses. Nevertheless it has served the purpose of all sensible hypotheses in stimulating research into the mode of action of this interesting compound which, as well as paralysing thousands of bootleggers' customers 20 years ago, has continued to injure those exposed to it during manufacture or from accidental contamination of food. From these beginnings new information may soon be acquired on the metabolism of the nervous tissues about the diseases of which we know so little.

The mysteries and problems discussed in this symposium were not confined to the action of anticholinesterases in the body. The biochemists studying the enzymes called cholinesterases have been forced to subdivide them still further according to their properties, thus raising new questions about their real function and the possibility that other esters of choline may have important roles in physiology. Even in the chemical field, where the biologist is inclined to think that everything is much more cut-and-dried, there seems to be no clear basis for deciding what will and what will not make a good inhibitor of cholinesterase or a good poison. The chemists' task is complicated by the fact that some of the compounds produced, having no apparent interest for the biochemist studying their activity against cholinesterase in the test-tube, prove extremely poisonous when injected into the body. The chemist must therefore be prepared for his own handiwork to be unexpectedly improved in a manner he does not yet clearly understand by the metabolic processes of the body. Such possibilities make it seem ever more unlikely that a clear relationship between chemical structure and biological action will become established.

The search for new and more unpleasant poisons will probably not be abandoned, but the medical man may draw a measure of satisfaction from the possibility that the study of them may increase our knowledge of how the body works, and hence our chances of understanding and correcting such disorders of its mechanism as are seen in disease.

TRAINING IN FORENSIC MEDICINE

The most vivid memories of student days are probably of the great teachers rather than of the great subjects in medicine—whichever they may later be thought to be. But forensic medicine, shot with its arresting criminal colours, is perhaps the one department of teaching where lecturer and subject may, in happy symbiosis, provide lasting instruction in a form so easily assimilable that what is being taught may not always be apparent. It is a common misconception among even enlightened academic planners that forensic medicine consists of stabbing, strangling, rape, and the homicidal *causes célèbres* in poisoning. This is far from the truth.

How much forensic medicine—and what sort of teaching—does the medical practitioner need? How much should he be taught as a student, and how much might reasonably be left for experience and postgraduate training should he later wish to practise this branch of pathology? The average doctor need know little of ballistics as a science, of the technical details of reconstruction of human remains, or of serological paternity tests, though he should know enough about them to enable him to co-operate usefully with a consultant called in to deal with a case. Forensic medicine has in the past been somewhat overweighted with tuition in matters best left to the expert. But every doctor must know what to do with a dead body, how to certify death and for cremation, when to ask for the assistance of the coroner or police, and how to collaborate with the law in the best interests of the public. He cannot afford to be ignorant of the law on poisons, abortion, or infanticide, or of his own legal and moral obligations in practice.

These are things on which he must have detailed instruction—as much for his own as for general security. The numerous inquiries received from practising doctors by departments of forensic medicine on medico-legal problems, and the increasing recourse to litigation by members of the public, give ample proof of the necessity for such instruction.

The universities have an important task in fostering both undergraduate and postgraduate training—so admirably fulfilled for long in Edinburgh and Glasgow, and now more recently in Leeds and, if only in one medical school, in London. Yet it has so happened that, just when a university department of forensic medicine has been established in one of the London medical schools, the decision has been made to eliminate forensic medicine as a separate subject from the final examination. The student may well overlook the significance of the subject and devote less interest to its teaching—a possibility that carries dangers both for himself and for his patients. The remonstrances of teachers in the subject were apparently overwhelmed by the claims made for the numerous other subjects to be represented in the final examinations.

While undergraduate teaching continues—as indeed it must—and is directed to the needs of future medical practitioners in their contact with the law, postgraduate instruction is being expanded, notably in Glasgow, Edinburgh, and London. In the last city about 8,000 bodies every year come within the jurisdiction of the coroners, and also available for instructional purposes are several school departments of pathology, one department of forensic medicine (with ancillary toxicological and physical laboratories), the public mortuary service, police surgeons' work, and the courts. The ideal arrangements are undoubtedly easier to achieve in a small city, for the population of London provides too many dead over too vast an area to make transport to one central institute of all types of dead a practical proposition. Nor is it necessary. Of 10,000 coroners' cases analysed for a Ministry of Health report towards the end of 1945, no fewer than 5,510 were ordinary natural deaths in which there had been no medical attention, a further 1,388 had some trivial injury, and 120 were "returned by the Registrar." The remainder lay in more forensic fields: 592 were "anaesthetic deaths," and 1,554 were due to accidents; 836 suicidal, poisoning, or criminal fatalities completed the total. What are required are good mortuary facilities with ancillary laboratory accommodation, the services of specially trained forensic pathologists, and part-time university posts for the senior among these, who, on the basis of their practical daily experience of special material, could devote part of their time to postgraduate teaching in the subject.

Forensic medicine strives to satisfy the growing need for preventing crime at its roots. It teaches practising doctors as well as more specialized pathologists to be ever watchful for "grounds for suspicion," wary of unsatisfactory certification, jealous of the moral and litigious security of the public whom it serves, and able to serve the law before the uniformed man is at the door. The doctor's work may only incidentally include criminal cases, but much of it is of a medico-legal character which demands skill and proper training, as much for the security of the doctor himself as for the public. It would be unfortunate if the training for this branch of medicine fell behind the needs of those who must practise it, whether as consultants or general practitioners.

TUBERCULOSIS AFTER PARTIAL GASTRECTOMY

The great advantage of surgical over medical treatment for peptic ulcer is that the risk of relapse is much reduced; even if the surgeon needs to qualify his assurance somewhat to the patient with a duodenal ulcer, he can confidently assert that a gastric ulcer will be permanently cured. The immediate mortality from surgical treatment is extremely low in the uncomplicated case, so that it is only the occurrence of a number of undesirable end-results, unrelated to the original disease from which the patient was suffering, that prevents partial gastrectomy from being adopted on a far wider scale than it is at present. Much has been written about the occurrence of anaemia and of the dumping syndrome after partial gastrectomy. The former can always be treated successfully, though it is sometimes not easy to do so. The latter, if it occurs, may be both persistent and unpleasant, and a number of new surgical techniques have been devised with the object of eliminating it—for example, Capper and Butler's[1] proposal to give anatomical support at the time of operation to the remnant of the stomach and to the afferent loop of the jejunum. Less interest has been shown in the loss of weight which occurs after radical gastrectomy in some 50% of patients, though it stands to reason that a lowered standard of nutrition might often adversely affect the patient's subsequent health. Pulvertaft[2] has reported that 8 patients out of 23 who died two to seven years after partial gastrectomy died of tuberculosis (7 of pulmonary and 1 of meningeal tuberculosis). Only 2 of the patients who died were known to have had the disease before the operation, and it is possible that the development of active disease in the others was brought about by impaired nutrition. Certainly the proportion of deaths due to tuberculosis is far greater than could be expected among a normal population of the age and sex distribution of Pulvertaft's series.

This is the most striking experience that has been reported, but other workers have also noted a disproportionately great number of deaths from tuberculosis. Bruusgaard[3] found 4 such deaths out of the 14 which occurred among patients discharged from hospital; and Drablos, Linden, and Skjelbred[4] found 3 among 30 deaths. Yet others have reported no deaths from tuberculosis, so that before any association can be accepted it will be necessary to ensure that the group of patients studied are properly representative of all patients who have been subjected to the operation. It may be,

[1] *British Medical Journal*, 1951, 2, 265.
[2] *Lancet*, 1952, 1, 225.
[3] *Acta chir. scand.*, 1946, 94, *Suppl.* 117.
[4] *Acta med. scand.*, 1951, 140, 327.
[5] *Lancet*, 1948, 1, 505, 551.

for example, that the extensive resection advocated by Visick,[5] and which had been performed on most of the patients referred to by Pulvertaft, is more conducive to the development of tuberculosis than the limited two-thirds to three-quarters gastrectomy performed by some other surgeons. It is also possible that the fundamental association is with poor economic status—which is known to be independently linked with both gastric ulcer and pulmonary tuberculosis. Nevertheless, enough evidence is available to make it clear that the final effects of partial gastrectomy cannot be assessed one or two years after the operation. Before it can be confidently recommended as the treatment of choice for young patients it is necessary to know what effect it may have on their lives 10 and even 20 years later—and about that there is, as yet, not enough information.

SMOKING AND CANCER OF THE LUNG IN DOCTORS

Further evidence of a causal connexion of some sort between smoking and cancer of the lung is reported in a recent issue of the *New England Journal of Medicine*. There Dr. E. L. Wynder and Mr. J. Cornfield describe[1] an investigation they have conducted into cancer of the lung in physicians, and the main conclusion of it is that they found a "highly significant association between the use of tobacco and the development of pulmonary cancer."

Their investigation was of a kind that could have been carried out only in the U.S.A. Each week the *Journal of the American Medical Association* publishes short obituary notices, nearly all of which record the cause of death. Selecting notices for the years 1950 and 1951 and the first two months of 1952 (and, for lung-cancer cases, 1949 also), Wynder and Cornfield sent letters containing a questionary to the estates of doctors listed as dying from cancer of the lung, colon, stomach, kidney, and bladder, and from leukaemia, lymphoma, and sarcoma. They finally had for analysis completed replies on 63 doctors recorded as dying from cancer of the lung, which comprised 58.9% of possible replies in that group, and completed replies on 133 doctors who died from other malignant diseases, which comprised 63.9% of possible replies in that group. The questionary included questions on smoking habits of the deceased doctor, on exposure to dust, fumes, and insecticides, and on the length of the responder's personal acquaintance with him.

The figures showed that in the lung-cancer group only 5.8% smoked on average less than 15 cigarettes or their equivalent a day as compared with 43.4% in the other-cancer group. As regards the heavy smokers, in the lung-cancer group 33.8% smoked 35 or more cigarettes (or their equivalent) a day, while in the other-cancer group only 12.7% did so. The period asked about in the questionary was the previous 20 years, and, though they do not explicitly say so, Wynder and Cornfield assume that the average daily amounts of tobacco they record as smoked were in fact smoked over the full 20 years. The distribution of doctors between town and country and of those specially exposed to dusts or insecticides did not vary significantly between the two groups.

The writers are aware that their method of gathering the data cannot lead to wholly reliable results. But, while the data are certainly incomplete, they are not likely to be so biased as to invalidate the conclusions. This paper adds confirmatory evidence to the previous work of Wynder himself[2] as well as of other investigators, including Doll and Bradford Hill in Britain.[3,4]

1 *New Engl J Med*, 1953, **248**, 441.
2 Wynder, E. L., and Graham, E. A., *J. Amer. med. Ass.*, 1950, **143**, 329.
3 *British Medical Journal*, 1950, **2**, 739.
4 Ibid., 1952, **2**, 1271.

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If the pioneers have a hard time in some ways, at least they may not have to spend those long hours hunting through the literature that their successors sometimes find irksome. And so voluminous has medical literature become in the last fifty years that guides have had to be devised—for example, by Morton[5] and Greenwood[6]—to help the inquirer find his way about it. Edited or select bibliographies of various kinds have also been published. Some cover the output of a single country, or the papers in a particular specialty, or the papers in a few selected journals.[7] A limited bibliography of this type has recently been published to record articles and books published in France in the last few years on diseases of the cardiovascular system.[8] The whole is in English, including a few abstracts of the more important papers, and Professor René Leriche surveys it in a preface.

On a much larger scale than these restricted lists, but avoiding the unwieldy proportions of a complete bibliography, *Abstracts of World Medicine* is published monthly by the British Medical Association. It selects from about 1,700 periodicals (or about 13,000 issues a year) those papers that seem to be of greatest interest or importance. Its subject and author indexes point to all the main papers on any medical subject soon after they are published, and also to many papers of subsidiary importance, while in the body of the journal short abstracts of them appear. As a guide to current literature, and not merely a compendium of it, the selection practised by *Abstracts* has been found by inquiry to be of special value. While the output of medical literature continues to expand each year—and it has been expanding steadily since the war—the function of an edited bibliography subserved by *Abstracts* becomes increasingly necessary if the inquiring reader is not to get lost.

The next session of the General Medical Council will open on Tuesday, May 19, at 2 p.m., when the President, Professor David Campbell, will take the chair and will deliver an address.

5 Morton, L. T., *How to Use a Medical Library*, 2nd ed. London: W. Heinemann 1952.
6 Greenwood, M., *J roy. Stat. Soc.*, Ser. A, 1948, **111**, 230.
7 Adams, S., *Bull med Libr Ass.*, 1950, **38**, 238.
8 *French Bibliographical Digest. Medicine: Heart and Blood Vessels.* No. 1M. 1952.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

ANTICOAGULANT THERAPY

BY

H. PAYLING WRIGHT, Ph.D., B.Sc., L.M.S.S.A.

Research Assistant, Obstetric Unit, University College Hospital Medical School

The modern treatment of all types of thrombosis is very different from that of twenty years ago. The changes are mainly dependent upon the introduction of anticoagulant drugs, which, by preventing the initiation or propagation of thrombi, are often able to save the condition of a patient from becoming critical. Unfortunately, both heparin and dicoumarol require scrupulous control if they are to achieve successful therapeutic results without producing haemorrhage, so that their use makes admission to hospital almost essential. Nevertheless, medical practitioners will wish to have a clear understanding of the mode of action of these drugs, their method of control, and their limitations.

In the past decade it has become evident that the Morowitz theory of blood clotting (prothrombin + calcium ions + thrombokinase = thrombin; thrombin + fibrinogen = fibrin) is insufficient to account for all the successive stages in coagulation. For instance, for its conversion to thrombin, prothrombin is now known to require at least four factors, while thromboplastin (thrombokinase) is recognized as occurring in a precursor form (thromboplastinogen) which is activated by an enzyme (thromboplastinogenase) derived from tissue autolysis and platelet disruption. Besides these factors, which can be reconciled with Morowitz's ideas, there are others, inhibitory to the clotting mechanism, which cannot be accommodated by his theory. Although in this article it is impossible to set out in detail current views on the mechanism of blood coagulation, it may be assumed that in the normal person the clotting process and its antithesis, the haemorrhagic process, are so nicely balanced that neither catastrophe occurs. It is on this delicate equilibrium that the anticoagulant drugs exert their effects.

Heparin

Heparin was the first of the anticoagulants to receive wide clinical use. It is a mucopolysaccharide derived from liver, lung, and other tissues, and is believed to compose the granules of the basophil leucocytes. It acts solely on the clotting substances already present in circulating blood, and this accounts for its rapid and transitory action and its effectiveness *in vitro*. Heparin has been shown to have several actions: it prevents the combination of fibrin and thrombin; it reduces the conglutination of platelets and so inhibits the liberation of thromboplastinogenase; and, finally, it has been shown to behave as an anti-prothrombin when coupled with a plasmatic complement fraction. It is thus apparent that this anticoagulant can interfere with coagulation in at least three ways.

Control of Treatment.—Since heparin acts directly upon circulating substances, an estimate of the clotting properties of the blood must be made before each administration. For this, the determination of clotting time by the Lee–White or similar technique gives a satisfactory, though crude, guide to therapy. (The prothrombin-time estimation is not a suitable test for this purpose.) As a general rule the prolongation of clotting time to three times its normal (five to seven minutes) suffices for therapeutic purposes, and this can usually be achieved by 10,000–15,000 international units of heparin, given intravenously every four hours. Slow-acting heparin preparations for intramuscular injection have been prepared, but, owing to variable rates of absorption, their action is erratic. Moreover, they are often extremely painful.

Haemorrhage Following Overdosage.—Should haemorrhage occur during treatment a 1% solution of protamine sulphate* may be injected intravenously in doses of 5–10 ml. Protamine reacts with heparin to neutralize the latter's negative electric charge, thus destroying its anticoagulant action. Blood transfusion may also be used to control bleeding, but in haemorrhage due to heparin fresh blood must be given, since stored blood lacks the labile factor necessary for prothrombin conversion. This factor is absent from the circulation during heparin therapy and must be replaced before normal coagulation can occur.

Dicoumarol and Allied Substances

A haemorrhagic and often fatal condition of cattle, known as "spoiled sweet-clover disease," led Link and his colleagues to investigate the chemical substances found in melilot ensilage. From this they isolated a substance—dicoumarol—which they showed to be a powerful anticoagulant, but which, unlike heparin, had to be ingested and passed into the blood stream before it exerted its action. Dicoumarol is without effect upon the clotting substances already circulating in the plasma, and hence has no anticoagulant action on blood *in vitro*. Its anticoagulant action depends upon its power to modify the ability of the liver cells to utilize vitamin K in the normally continuous synthesis of prothrombin, and this alteration in prothrombin production impairs the clotting mechanism at this level. For this reason, dicoumarol acts slowly, since time is necessary for its absorption from the gut and for the prothrombin already in circulation to undergo its natural depletion.

Control of Treatment.—Treatment with dicoumarol and kindred derivatives is usually controlled by means of Quick's single-stage prothrombin-time estimation. Though this test probably measures other variable factors besides free prothrombin, it offers a safe and easy method of assessing the response of the coagulation mechanism to anticoagulants of the dicoumarol type. The whole-blood clotting-time test used in heparin control is relatively insensitive to alterations in prothrombin concentration, and is therefore unsuitable for the management of dicoumarol therapy. Nevertheless, the prothrombin-time test is not without its pitfalls, and a rigid technique must be employed. Many modifications of the method are in current use, some of which are now recognized as unreliable, and in order safely to control dicoumarol administration it is essential to use a sensitive technique and to know the extent to which results may be effected by personal and environmental variations. When these factors are satisfactorily standardized, a comparison of the patient's prothrombin time during therapy with his own premedication figure or with that of a normal subject gives a satisfactory method of assessing the response to the drug. To enable results from different laboratories to be compared they may be expressed as percentages of normal prothrombin activity. This can be done by constructing a time-concentration curve for "normal" blood with the technique employed in the particular laboratory. Such a curve is obtained by measuring the prothrombin times in serial dilutions of normal whole citrated plasma. These times are plotted against the dilution expressed as a percentage of the initial plasma. This method of recording results is now widely used.

Method of Administration.—The response to dicoumarol administration is slow, 16 to 24 hours elapsing before blood changes become apparent, while the maximal effect is seldom reached before 30 to 40 hours after ingestion. Cumulative

*1 ml. of 1% solution of protamine sulphate = 1,000 international units of heparin.

effects may therefore be encountered, and for this reason prothrombin activity should be measured at the end of the first 24 hours and subsequently daily. About one in ten persons is resistant to dicoumarol and requires a greater dose or more prolonged administration to achieve the desired fall in prothrombin level; these cases need particularly careful control if haemorrhage is to be avoided. An average plan of dosage for dicoumarol is 300 to 400 mg., in divided doses, during the first 24 hours; 200 mg. during the second 24 hours; and thereafter 50 to 100 mg. daily as maintenance dose. In most patients this will reduce prothrombin activity to 25 to 35% of normal by the end of the third day. It must be emphasized, however, that derivatives such as ethyl biscoumacetate ("tromexan") and cyclocoumarol and such substances as phenylindanedione have their characteristic rates of absorption, and consequently different dosages. When the prothrombin activity has been reduced to 25 to 35% of normal for some days a dose can usually be determined which will maintain it steadily at this level. It is then safe to reduce the frequency of prothrombin-time estimations to every second day for the next week. Should no marked fluctuations occur during this time, the interval between the tests may be still further extended. However, fluctuations may occur even in a "balanced" patient, and if control tests are infrequent the risk of serious haemorrhage becomes greater.

Out-patient Treatment.—The question of out-patient treatment with the dicoumarol anticoagulants is a vexed one. In my opinion it is permissible only if the following precautions are strictly observed: (1) the patient remains in hospital until satisfactorily balanced while fully ambulatory; (2) the prothrombin activity is not depressed below 25% of normal; (3) prothrombin-time determinations are carried out *at least* once a week; and (4) no drugs are administered except with the knowledge of the physician in charge of anticoagulant therapy. Even under these stringent conditions, the danger of spontaneous or traumatic haemorrhage is considerable, and the practitioner should explain this risk to the patient. Haematuria is the commonest first sign of overdosage with dicoumarol and similar anticoagulants.

Haemorrhage Following Overdosage.—When overdosage with dicoumarol or kindred substances has occurred, the resulting haemorrhage can be controlled by blood transfusion. Since the prothrombin-activation factor which is absent in stored blood (Quick's "labile factor") is not the same as that which is lacking from the patient's plasma during dicoumarol therapy (Quick's "component B"), the blood of the recipient and stored blood from a donor are complementary; the patient's prothrombin-activating complex is therefore reconstituted equally as fully by the giving of stored as of fresh blood. Transfusion must be continued until the absorption of anticoagulant from the gut has come to an end and normal prothrombin constituents have been restored in the blood. The efficacy of water-soluble vitamin K, either orally or by parenteral injection, in the control of haemorrhage following dicoumarol is controversial. Recently, however, a purified form—fat-soluble vitamin K_1—has been prepared which restores the prothrombin from the haemorrhagic to the normal level within four to eight hours. The mode of action of the vitamin is obscure, but may nevertheless prove a powerful antidote in dicoumarol overdosage.

Indications for Anticoagulant Therapy

Coronary Occlusion.—The value of anticoagulants in preventing immediate propagation of coronary thrombi or the development of further episodes was investigated by the American Heart Association in 1946. The material from 16 large hospitals was reviewed by a panel of investigators who concluded that the results with this type of treatment were highly favourable. Both heparin and dicoumarol were used, often in conjunction, the heparin usually being given only until the prothrombin level of the blood was satisfactorily depressed by the dicoumarol given concurrently. When this level was reached the heparin was withdrawn and the patient maintained on dicoumarol alone. When anticoagulant therapy was given the mortality was reduced to about two-thirds that of a control group which received conservative treatment only. This advantage was most marked during the first four weeks after the primary coronary episode. The number of thrombo-embolic complications elsewhere in the body during convalescence was also reduced to one-third that in the control group. Anticoagulant therapy must be considered as prophylactic, since it has no effect upon the progressive development of arteriosclerosis, though both heparin and, to a greater degree dicoumarol, have been stated to increase the coronary flow. Moreover, recent experimental work has shown that, in rabbits, artificially thrombosed arteries are recanalized sooner when a steady hypoprothrombinaemia is maintained.

*Pulmonary Embolism.**—Intravenous heparin, followed by dicoumarol, should be given as soon as possible after embolism has occurred, so as to reduce the likelihood of further catastrophes. When propagation of the thrombus at the site of origin has been prevented the danger of detachment is much reduced.

Vascular Surgery.—When operations on large arteries are undertaken, heparin often aids in preventing thrombi forming at the site of surgical intervention.

Auricular Fibrillation.—Since mural or auricular thrombi frequently give rise to emboli when auricular fibrillation is reversed by quinidine, the risk of this complication can be much reduced by anticoagulant therapy. Prothrombin activity should be reduced to about 25% of normal, and this level should be maintained for at least five days before quinidine reversion is attempted.

Post-operative and Puerperal Venous Thromboses.—These cases respond most satisfactorily to anticoagulant therapy. Treatment is indicated when venous thrombosis has occurred in the deep veins of the leg. Prophylactic treatment may also be given to patients who have experienced previous thromboses or in whom there are predisposing factors which lead the practitioner to fear the formation of thrombi. The judicious use of anticoagulants will reduce the danger of pulmonary embolism. Venous thrombosis during pregnancy may safely be treated with dicoumarol-like substances, provided the prothrombin level is not depressed below 30% of normal. The drug should be withdrawn for at least one week before delivery is expected, both to minimize the risk of uterine haemorrhage and to ensure that the prothrombin level of the infant at birth shall not be dangerously depressed. In the puerperium, anticoagulants of the dicoumarol group can safely be administered prophylactically or when venous thrombosis has already occurred. Lochial loss is not increased if the prothrombin is maintained at the usual therapeutic levels, nor at these levels are anticoagulants secreted in the milk in sufficient quantity to affect the suckling infant.

Retinal Vein Thrombosis.—Favourable reports on the use of both heparin and dicoumarol in retinal vein thrombosis have been made, but the data available are still very meagre.

Contraindications to Anticoagulant Therapy

Immediately after Surgery.—In the treatment of surgical cases it is advisable to withhold heparin for at least 12 hours after operation. This allows time for the formation and firm attachment of thrombus plugs in the small vessels at the site of operation to take place. Dicoumarol and its derivatives can more safely be started immediately after surgery because the lag in their action allows the completion of these processes. If there is a large denuded operation site, or if ulceration or local infection is present, the risk of haemorrhage with anticoagulant therapy is much increased.

Abnormal Prothrombin Metabolism.—Exaggerated responses to anticoagulants of the dicoumarol type sometimes

*For further information on this subject see *Venous Thrombosis and Pulmonary Embolism*, by A. Neuhof (1943: Grune and Stratton, New York), and *Thrombotic Conditions and Their Treatment with Anticoagulants*, by C. D. Marple and I. S. Wright (1950: Blackwell, Oxford).

occur. All patients with conditions in which vitamin-K absorption or production is defective, and especially those with disorders of fat digestion, are notably sensitive to oral anticoagulants. These include cases of dietary deficiency or biliary dysfunction, diarrhoea and enteritis, sprue, steatorrhoea, and resection or ulceration of the intestinal tract. Alterations of the intestinal flora brought about by drugs may also cause hypoprothrombinaemia, sometimes to a severe degree. Certain drugs, other than anticoagulants, also lower the prothrombin level of the blood, and are thus synergic in their action. The commonest are the salicylates, though caffeine, theophylline, and theobromine behave in the same way. These drugs should not be given concurrently with oral anticoagulants. Normal prothrombin production may be impaired in persons whose liver function is disturbed, so that some degree of hypoprothrombinaemia may be already present. The administration of dicoumarol to cases with Laennec's cirrhosis, infective hepatitis, carcinomatosis, or liver abscess is followed by an exaggerated response.

Renal Damage.—Impairment of renal function is a contraindication to the use of anticoagulants for two reasons. First, cumulative effects are more apt to develop, so that the danger of haemorrhage is increased. Secondly, renal vessels are particularly vulnerable, as they often prove the first site at which haemorrhage occurs in hypoprothrombinaemia. If the kidney is already injured this danger is further increased.

Next Refresher Course Article.—"Hysteria," by Dr. I. R. C. Batchelor.

IMPERIAL CANCER RESEARCH FUND

The fiftieth annual report of the Imperial Cancer Research Fund was presented at the general meeting of governors held at the Royal College of Surgeons on April 23, the chairman of the council, Professor H. R. Dean, presiding. Mr. A. Dickson Wright, honorary treasurer, said that for the first time in the history of the fund the assets totalled over £1,000,000. Excluding legacies, which amounted to £97,500, the contributions during the year 1952–3 came to close upon £25,000, an increase of £13,000 on the figure for the previous year, and the long list of subscribers illustrated the wide interest shown in cancer research. The general working expenses, however, had increased, leaving an excess of expenditure over receipts of £5,500. The large increase of expenditure was in connexion with the provision for the clinico-pathological investigations which were initiated in 1951, and had made it necessary to obtain additional laboratory space at Lincoln's Inn Fields.

Professor Dean presented the general report on the work of the fund. These new clinico-pathological investigations, which had been placed under the general supervision of Professor Geoffrey Hadfield, would increase the scope of the research work, and the institution of a second laboratory would offer excellent opportunities whereby the clinico-pathological research and the basic research into cancer might, as they should, supplement and stimulate each other. Plans had been drafted which would make it possible to establish four large research laboratories, to come into operation in July of this year, and two additional laboratories would be available in the spring of 1954. This research accommodation would provide laboratory space for at least six research workers. The special investigations which have been taken in hand relate principally to cancer of the breast and of the prostate.

The president of the fund, the Earl of Halifax, was re-elected, as was the honorary treasurer, Mr. Dickson Wright. Tributes were paid to three distinguished workers for the fund whose deaths had occurred during the past year—namely, Sir Holburt Waring, for many years treasurer, Professor W. E. Gye, the former director, and Dr. Charles Kellaway, a member of the council.

MEDICAL EXAMINATIONS FOR NATIONAL SERVICE

The proportion of young men who are found to be unfit when called up for National Service is about 18%. These are the men who are placed in Grades III and IV by the medical boards; most are rejected for service, but some in Grade III are accepted for the lighter jobs. When these figures were announced to the subcommittee of the Select Committee on Estimates, which has been considering, from the standpoint of economy, the question of call-up, posting, and movement of National Service men, they were described as "fantastic" and "alarming"; but, of course, as a witness from the Ministry of Labour pointed out, everything depends on the standards adopted. The proportion of candidates for the Regular Army who fail on medical grounds is much greater; one witness spoke of "somewhere in the region of 40%." The Committee's report[1] gives some interesting details about the working of the National Service medical boards, of which there are 61 in Great Britain. Each board consists of a chairman and four members, all civilian doctors, and the chairman has power to seek consultant advice where necessary. It is estimated that the examination of a recruit by each doctor in turn occupies on the average seven minutes. One point brought out in the evidence is that only three-fourths of the men are subjected to *x*-ray examination. This is because of shortage of apparatus and staff difficulties in the remoter parts of the country. Men who have not had an *x*-ray examination at their medical board are radiologically examined fairly soon after entering the Service. For economic reasons the subcommittee deplores this and recommends that Service *x*-ray equipment should be made available for use by the medical boards, and that urgent steps be taken to increase the number of civilian *x*-ray units.

When a man, having passed the medical board, joins the Service an initial military medical examination is made, normally by the unit medical officer, who has before him the form of assessment issued by the board: The number of men discharged on medical grounds during their first 14 days of service is a measure of the difference of opinion which exists between the civilian medical board and the military medical officer. This difference is very slight except in the case of psychiatric disabilities, which, of course, the board is not well placed to detect, seeing that they manifest themselves in anomalies of behaviour and not in physical signs. In 1951 the number of discharges of National Service men from the Army during their first fortnight was 7 per 1,000 of intake, and in rather more than half of these the discharge was on psychiatric grounds (meaning, as one witness stated, nearly always "mentally slow").

The report also contains an important recommendation with regard to intelligence tests. Before his medical-board examination each man undergoes an "intelligence test" supervised by Army sergeants, and the results of these tests and of any interviews which may follow them are reported to the chairman of the medical board. Stress was laid by War Office witnesses on the simplicity of these tests. No exercise of judgment or foundation of experience, apparently, is called for. But a large proportion of the gradings made by these Army testers are subsequently altered by the boards, and the subcommittee holds that there is no reason for the employment of Service men on this work at all. Any testing of this kind would be more advantageously done by specially trained civilian men or women acting under the supervision of the chairmen of the boards, and a common series of intelligence tests should be worked out by the Ministry of Labour and the Service departments in consultation.

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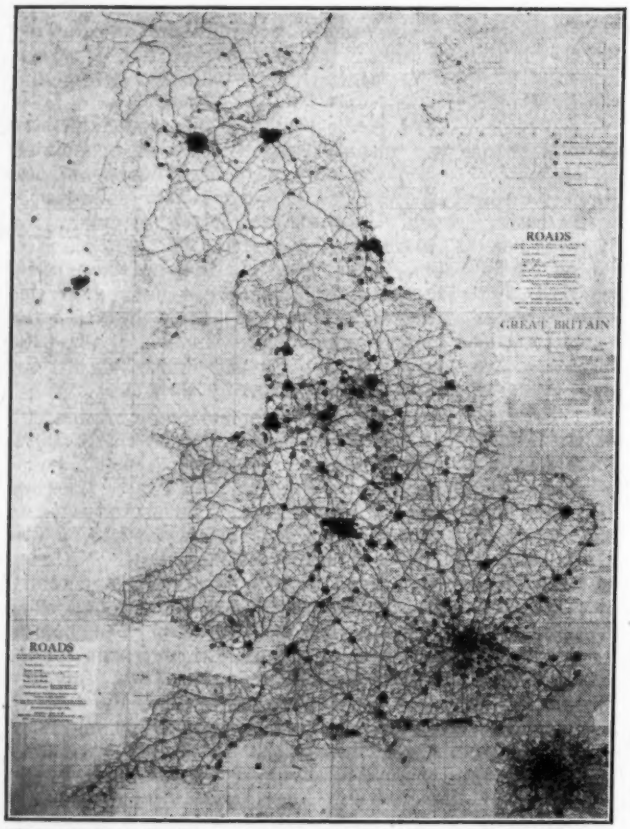
[1] *Third Report from the Select Committee on Estimates, together with Minutes of Evidence taken before Subcommittee C and appendices.* "Call-up, Posting, and Movement of National Service Men." London: H.M. Stationery Office. 4s. 6d. net.

COLLEGE OF GENERAL PRACTITIONERS

In its most recent statement (*British Medical Journal*, March 28, p. 725) the College of General Practitioners announced that its peripheral activities would be organized by a number of Regional Faculties. Below are printed the names of the Faculties and the areas which it is proposed that they should serve. As in some cases county boundaries or regional hospital board areas may prove inconvenient, members or associates of the College will be free to choose to which Faculty they should belong.

Regional Faculty	*Area Served*
	England
London	County of London
Home Counties South	Kent, Surrey, Sussex, Hampshire and the Isle of Wight
Home Counties North	Middlesex, Essex, Hertfordshire, Bedfordshire
Oxford	Oxfordshire, Berkshire, Buckinghamshire
Cambridge	Cambridgeshire, Huntingdonshire, Norfolk, Suffolk
Bristol	Wiltshire, Gloucestershire, Somerset, Dorset
Exeter	Devon and Cornwall
Birmingham	Warwickshire, Shropshire, Herefordshire, Worcestershire, Staffordshire, Leicestershire, Rutland, Northamptonshire
Sheffield	Derbyshire, Nottinghamshire, Lincolnshire
Leeds	South Yorkshire (West and East Riding)
Manchester	North and East Lancashire (East of the London–Glasgow Road A.6), East Cheshire, Westmorland
Liverpool	South-west Lancashire, West Cheshire, North Wales and the Isle of Man
Newcastle	Durham, North Riding of Yorkshire, Northumberland, Cumberland
	Wales
Cardiff	South Wales, Monmouth
	Scotland
Edinburgh	South-east Scotland
Glasgow	South-west Scotland
Dundee	East Scotland
Aberdeen	North-east Scotland
Inverness	North Scotland
	Northern Ireland
Belfast	
	Southern Ireland
Dublin	
Galway	



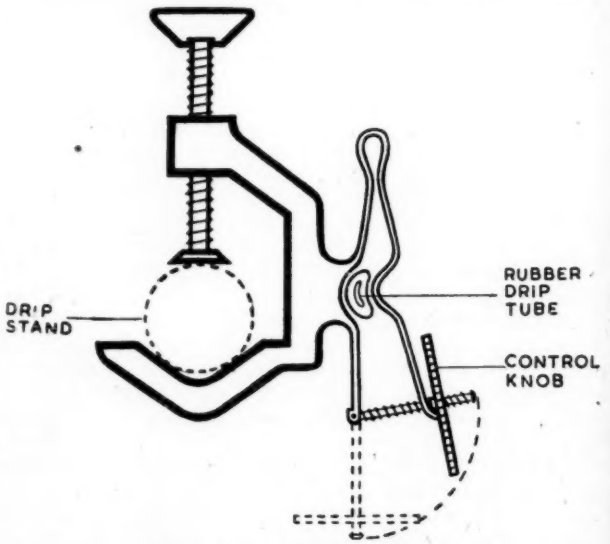
Map showing distribution of Foundation Membership (1,087) of the College of General Practitioners on March 31, when the College was three months old. The black dots in the small square in the right-hand corner represent membership in London in addition to those on the larger map. The Ordnance Survey Map is reproduced with the sanction of the Controller of H.M. Stationery Office (Crown copyright reserved).

Will members or associates who wish to make suggestions or comments upon the areas covered by these Regional Faculties please write to the secretary, the College of General Practitioners, 14, Black Friars Lane, Queen Victoria Street, London, E.C.4.

Preparations and Appliances

A FINE ADJUSTMENT INTRAVENOUS DRIP REGULATOR

Dr. H. J. V. MORTON, senior anaesthetist, Hillingdon Hospital, writes: The modern practice of giving potent short-acting drugs by the method of continuous intravenous infusion has created the need for a drip regulator capable of fine adjustment. Such an apparatus is illustrated here. It is intended for use with standard intravenous outfits, and has advantages which are self-evident. The finely threaded control knob swings sideways to allow the introduction of the rubber tube. The light alloy clamp opens to 1⅜ in.



(35 mm.), and grips the thinnest armboard or thickest drip stand. When used in the latter situation it should, of course, be fixed level with or lower than the infusion needle.

The drip rate can be easily altered by as little as one or two drops a minute, a degree of control valuable to the paediatrician. When used during anaesthesia, in conjunction with a rotameter or variable pendulum indicator (Morton, 1953), dosage can be adjusted quickly, precisely, and with one hand.

The instrument is strongly made, and is obtainable, with or without the clamp, from Blease Anaesthetic Equipment, Ltd., 12, Hinde Street, London, W.1, to whom my thanks are due.

REFERENCE

Morton, H. J. V. (1953). *Anaesthesia*, **8**, 112.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Procaine Amide

SIR,—Since our attention was drawn some time ago by Dr. G. E. H. Enderby to the use of procaine amide to augment the hypotensive action of hexamethonium, described by Dr. A. A. Mason and Dr. J. F. Pelmore (*Journal*, January 31, p. 250), we have investigated some of its pharmacological properties. The action of procaine amide has usually been discussed with respect to its direct cardiac action. But, since procaine itself is well known to be able to interfere with ganglionic transmission, a study of the effects of procaine amide on ganglia seemed necessary.

We have found in cats anaesthetized with chloralose: (1) that procaine amide in doses of 15 mg./kg. or more will cause relaxation of the nictitating membrane excited by preganglionic stimulation; (2) that in doses of 15 mg./kg. it will paralyse the slowing of the heart to vagal stimulation; (3) that in doses of 15–30 mg./kg. it does not lessen the depressor effect of acetylcholine or the pressor effect of adrenaline; (4) in doses of 15 mg./kg. or more it reduces the pressor effect of nicotine. In concentration of 20–50 μg./ml. it reduces the contraction of the guinea-pig's small intestine to nicotine without affecting its response to acetylcholine. These observations indicated that procaine amide can interfere with ganglionic function in three ganglia at least, the superior cervical ganglion and the vagal ganglia of the heart and viscera, without modifying the reactions of the effector cells. It remained to determine the mechanism of action.

Procaine amide, 10 mg., injected during perfusion of the cat's superior cervical ganglion caused complete failure of transmission and abolished release of acetylcholine on preganglionic nerve stimulation. With the perfused ganglion, procaine amide antagonized the stimulant effect of acetylcholine on the ganglion. Using the electrical recording of ganglion action potentials, procaine amide was found to be able to reduce these considerably without causing any depolarization of the ganglion. These results show that procaine amide has two actions at the ganglion-inhibition of acetylcholine release, and an antagonism to the effects of acetylcholine. The second of these two actions should, of course, simply sum with that of hexamethonium, if the two drugs are given together. But the interaction of the first action, that of preventing acetylcholine release, with the acetylcholine-antagonizing power of hexamethonium, might present novel features. We find, in fact, that in the cat procaine amide and hexamethonium potentiate one another, and that the effect of a mixture is greater than that expected from simple addition of the two components.

It seems probable, therefore, that this synergism between depression of acetylcholine release and competition with acetylcholine could go some way to explain the clinical synergism observed. The question arises whether any of the hypotensive action of procaine amide can be attributed to a direct cardiac action. Our only evidence on this point suggests that, in the cat, this is not true, since the relative potency of procaine amide to hexamethonium in lowering blood pressure is actually less than its relative potency in relaxing the nictitating membrane.

Procaine amide appears to offer, therefore, a new possibility of supplementing the action of a ganglion-blocking agent with a drug active by mouth, with which it might be possible to attack ganglia at present relatively refractory to such agents.—We are, etc.,

W. D. M. PATON.
J. W. THOMPSON.

London, W.C.1.

A.C.T.H. and Tuberculous Meningitis

SIR,—The results of the treatment of acute disseminated encephalomyelitis with A.C.T.H. by Dr. H. G. Miller (*Journal*, January 24, p. 177) interested me very much, as I am working on similar lines, except that I am applying this treatment in cases of tuberculous encephalomeningitis, against the warning of this author, who supposes that therapeutic use of A.C.T.H. in tuberculous meningitis "might well be disastrous."

My experiments are limited to those cases of tuberculous meningitis in children, treated with antibiotics, which develop acute neurological symptoms in the late period of treatment (after 10 weeks). The clinical behaviour of such cases is very similar to the symptomatology of acute disseminated encephalomyelitis. Here also we observe violent attacks followed by periods of relaxation, and we too suppose that they are caused by attacks of "allergic vasculitis" on the basis of a hypersensitive reaction of altered blood vessels of the brain. Lowered chloride levels in the C.S.F. in such cases suggests that oedema of the brain may follow or accompany the changes in the blood supply. This syndrome occurs in about 50% of our cases of tuberculous meningitis treated with antibiotics. They are refractory to further application of chemotherapeutics and their mortality rate is about 70%. In despair we tried A.C.T.H. in such cases. The effects are very encouraging, especially if A.C.T.H. is applied after previous preparatory administration of intrathecal tuberculin. We give 10^{-7} solution purified protein derivative tuberculin intrathecally every 2–3 days, in successively increasing doses—0.2, 0.4, 0.6, 0.8, and 1 ml.—then 10^{-6} in the same way until a distinct inflammatory reaction in the C.S.F. is provoked as shown by a pleocytosis and increase of protein level. Then the purified protein derivative administration is stopped and A.C.T.H., 15–25 mg., is given intramuscularly four times daily. The mortality rate among children so treated fell from 68% to 33%. In cases of blockade of the circulation of the C.S.F., A.C.T.H. reduces the protein level of C.S.F. and very often re-establishes free communication.

During combined treatment with tuberculin and A.C.T.H. no chemotherapeutics are given.—I am, etc.,

B. HALIKOWSKI,
Paediatric Department of the Tuberculosis Institute.

Warsaw.

"Butazolidin"

SIR,—In your leading article on "Benefits and Dangers of Butazolidin" (December 27, 1952, p. 1401) you commented on the toxic reactions to the drug, particularly emphasizing the risk of damage to the haemopoietic system. The following case may therefore be of interest.

A woman, aged 24 years, who had suffered from rheumatoid arthritis for many years, was given a course of butazolidin, 200 mg. twice a day, from February 9 to February 18. On February 17 she complained of a sore throat and feverishness. A provisional diagnosis of scarlet fever was made and the patient was given a course of sulphadimidine, 1 g. four-hourly, during February 19–23 without any improvement in her condition. She was therefore admitted to hospital on February 24.

On admission the patient was afebrile and was found to have slight inflammation of her fauces, associated with a generalized erythema. A throat swab was taken, but no haemolytic streptococci were isolated. A white cell count on February 25 gave 1,800 cells/c.mm., with 50% polymorphs and 50% lymphocytes. In view of the neutropenia, a further count was done on February 26, which gave Hb 9.2 g.%, red blood cells 4.46 million/c.mm., white blood cells 4,500/c.mm., neutrophil polymorphs 34%, eosinophil polymorphs 3%, lymphocytes 58%, monocytes 5%, platelets 340,000/c.mm. The sore throat persisted for 12 days and the rash for 15, following which there was desquamation. The patient remained afebrile during her stay in hospital. The following white cell counts were done before she was discharged on March 14: March 3, white blood cells, 5,100/c.mm., 44% polymorphs; March 6, white blood cells 4,400/c.mm., 36% poly-

morphs; March 11, white blood cells 5,700/c.mm., 62% polymorphs.

The only other drug treatment this patient had had for the rheumatoid arthritis within the previous four months, apart from the butazolidin, was aspirin.—We are, etc.,

G. E. BREEN.
R. T. D. EMOND.

Isleworth, Middlesex.

SIR,—In view of the widespread use of butazolidin for the relief of rheumatic symptoms I draw attention to another death following its administration.

A man of 59, with chronic bronchitis and rheumatoid arthritis of eight years' standing, began taking one tablet of butazolidin twice daily (400 mg. daily) on January 31. It substantially relieved his pain and enabled him to continue working. On March 13 he was "feeling fine" and was full of praise for his new tablets. His white blood count was 12,100, and showed a slight neutrophilia. His treatment was continued, but he was next seen after admission as an acute emergency on April 7. He had been ill for four days, and was then cyanosed, intensely dyspnoeic, and his circulation was failing. He had a massive consolidation of the left lower lobe, and examination of peripheral blood smears showed an absence of granular cells. He died 14 hours after admission.

It is likely that butazolidin contributed to his death, and the case emphasizes the importance of performing a white blood count *immediately* should a patient taking the drug develop fever or any other symptom of constitutional illness.—I am, etc.,

G. R. NEWNS.

Sheffield.

A New Diphtheria Prophylactic (N.A.F.T.)

SIR,—Since reporting the results of the experiments published in the *Journal* (February 14, p. 370) it appeared from further experiments done in guinea-pigs that different batches of the natural adjuvant varied from one another in their power of augmenting the antigenicity of purified diphtheria toxoid. It was also observed that each batch of the natural adjuvant had a definite optimum. If added to the toxoid in quantities either less or more than this optimum, the protection offered to the guinea-pigs against the challenge of the toxin by such mixtures appeared to be less than that offered by the optimum mixture. It is necessary, therefore, when testing the adjuvant power of a new batch of N.A.F. to employ several different quantities of the dried material—say 0.2 mg., 0.35 mg., 0.5 mg., and 0.65 mg. per Lf of the purified toxoid—instead of any one chosen quantity, and to compare the protection given by each of these different mixtures with that given by the toxoid alone.—I am, etc.,

D. C. LAHIRI.

Bombay, India.

Mental Hospital Service

SIR,—I hope that Dr. Otho FitzGerald's letter (*Journal*, April 4, p. 781) will attract the attention it deserves, particularly among the junior staff in mental hospitals. There is a growing tendency to concentrate all the hospital's resources on the acute and recoverable patient and to neglect and ignore the chronics. Fortunately this attitude does not apply to all mental hospitals. Following the lead given by Dr. T. P. Rees at Warlingham Park, at least one other hospital has inaugurated a scheme for the rehabilitation of the chronic patient which has revolutionized the atmosphere in the chronic wards, stimulated the interest and imagination of the nursing staff, and literally brought back to life many patients who otherwise would have led a purely vegetative existence to the end of their days.

But all this cannot be done without the active interest and co-operation of the physician superintendent. The National Health Service has done a grave disservice to mental hospitals by encouraging superintendents to discard their administrative responsibilities and to concentrate almost exclusively on clinical psychiatry. The result of this change has been that young men entering the mental hospital service now learn nothing of the administration of the hospital and are ignorant of the facilities available for the occupation of chronic patients in the various utility departments of the hospital. Comparatively few patients are employed on farms and gardens, yet many psychiatrists would agree that they can provide the best possible form of occupational therapy for a large number of chronic patients. Another disquieting feature is that the hospital has often ceased to be "a happy ship." Friction between lay administrators and medical staff arises, and there is a constant shifting of responsibility through all grades and divisions right back to the regional board.

I maintain that a mental hospital is so constituted that there must be one individual who is responsible to the committee for everything which happens within the hospital. He must be fully conversant both with the administrative problems and with modern psychiatric methods—a benevolent patriarch to whom all can turn for help and advice. There should be no interference with the clinical autonomy of other consultants, but at the same time the superintendent should have proved his ability as a clinical consultant himself so that his opinion would be respected and perhaps even sought when special difficulties arose. In other words, physician-superintendents should be appointed from senior consultants who have also a flair for administration and the teaching of postgraduate students. Naturally, their remuneration should be adjusted to compensate for the additional responsibilities which would attach to the job.

I shall probably be accused of advocating a reactionary measure. This would not be so if sufficient care were taken in the appointing of new superintendents only from applicants of the highest calibre, and such would, in my opinion, be attracted only if the job were up-graded in the way here suggested. A recent advertisement read: "Whole-time Consultant Psychiatrist. The appointment carries the Medical Superintendentship of ——— Mental Hospital." Obviously the medical superintendent is regarded as subordinate to the consultant. Unless we reverse this relationship the chronic patient is doomed.—I am, etc.,

J. C. SAWLE THOMAS.

London, W.1.

Prolapse

SIR,—I found Mr. A. J. Wrigley's refreshing account of prolapse (*Journal*, April 4, p. 778) most complete and satisfying. The only sentence that I would quarrel with is his statement that "the diagnosis of prolapse is easy." In most cases this is so, but often the painful symptoms of prolapse occur before the patient or her doctor have become aware of any uterine descent. By painful symptoms I mean that low backache and dragging in the groins which may be troublesome only at period time and is sometimes mistaken for dysmenorrhoea. These early symptoms are presumably due to stretching of the parametrial supports, and, like the pain of flat foot, is most marked when stretching is occurring, disappearing later when the prolapse is fully developed.

Diagnosis of prolapse at this early stage by the usual method of inspection during straining may be impossible if there is a good perineal support. There will then be no gaping at the introitus to reveal the descent of the cervix. Thus, if the symptoms suggest prolapse, it is advisable to retract the perineum with a Sims speculum while the patient lies in the left lateral position, and straining may then show an obvious descent of the cervix. If the uterus is retroverted this will be particularly liable to occur, and the backache of retroversion is due to this concomitant prolapse. The diagnosis in these less obvious cases may finally be made only by the empirical use of the pessary.—I am, etc.,

A. L. DEACON.

Birmingham.

Transverse Arrest of Head

SIR,—Mr. Bryan Williams is to be congratulated on his excellent account (*Journal*, April 18, p. 865) of the mechanism and treatment of transverse arrest of the head and occipito-posterior position. It is high time undergraduate teaching of the mechanisms of labour abandoned the idea that the usual engagement of the head is in an occipito-anterior or occipito-posterior position. Another concept that should be stressed more in teaching is the factor of pelvic shape rather than primary deflection of the head as a cause of posterior rotation of the occiput.

In describing the application of Kielland's forceps Mr. Bryan Williams states that only two fingers are needed to introduce the blades. In my limited experience it seems that where transverse arrest has occurred there often remains a loose rim or lip of cervix between the head and the sacral promontory, and I have always found it necessary to introduce a hand to be certain that the blades pass inside the cervix, especially as the handle must be carried far back to enable the tip of the blade to clear the promontory and slide up round the head. In De Lee's illustration of the manœuvre[1] it is true that only two fingers are ensuring that the blade passes safely, but the whole hand is within the vagina.—I am, etc.,

Northampton. E. A. J. ALMENT.

REFERENCE

[1] *Principles and Practice of Obstetrics*, 1947, 9th ed., p. 907. Philadelphia.

Intercourse after Syphilis

SIR,—It is tempting to allow Dr. P. Durel's letter (*Journal*, April 11, p. 838) to stand as an answer to your expert's letters, because, after saying that he has seen no relapse later than six months after such treatment as he and colleagues now give, he hedges with quite a strenuous treatment if the spouse becomes pregnant; it reminds one of the captain of the *Pinafore*: "Well, hardly ever." Having regard to the scarcity of new syphilitic infection in, at any rate, this country, until the results are known of such co-operative studies of the effects of modern treatment of syphilis as are now proceeding under the auspices of the World Health Organization in this and other countries neither your expert nor any other individual syphilologist can say what is the longest period after which no relapse has occurred. And a patient in relapse is sexually as contagious after one form of treatment as after another if the relapse is within the first two years of infection.

Dr. Durel concedes in effect the point which I made—that, psychologically, syphilis can be a life sentence—yet he advocates risking it and seems to write as if we who advocate a longer period of observation wish to make this longer than that imposed after arsenical–bismuth treatment. Anyhow, I do hope that neither will so advise any man who is to marry or has married any girl in whose welfare I am interested.—I am, etc.,

London, S.W.1. L. W. HARRISON.

Intestinal Polyposis Associated with Oral Pigmentation

SIR,—May I comment on the medical memorandum (*Journal*, March 21, p. 659) of Drs. I. Kaplan and M. Feuchtwanger on this subject? They state that this syndrome was first described by Jeghers in 1944. Fisher,[1] in his report of a case, correctly gave the credit for the original description to Peutz,[2] by whose name the condition is sometimes known (syndrome of Peutz).—I am, etc.,

Belfast. R. D. G. CREERY.

REFERENCES

[1] *Great Ormond Street Journal*, 1951, **1**, 151.
[2] *Ned. Maandschr. Geneesk.*, 1921, **10**, 134.

Chemotherapy of Malaria and Trypanosomiasis

SIR,—In the paper on "The Chemotherapy of Malaria and Trypanosomiasis" by Dr. L. G. Goodwin (*Journal*, February 7, p. 311) no differentiation is made between the treatment of infections due to *Trypanosoma rhodesiense* and those due to *Trypanosoma gambiense*. This is a common error found in nearly all the textbooks of tropical medicine.

Early cases of *T. rhodesiense* (that is, cases diagnosed within three weeks of the onset) always do respond satisfactorily to treatment with suramin ("Bayer 205," "antrypol"). There is, in my opinion, no justification for imperilling the chances of recovery of the patient by losing valuable time in trying other drugs.

Early cases of *T. rhodesiense* do not respond satisfactorily to treatment with pentamidine. In 1940 I treated three cases of *T. rhodesiense* at the request of Warrington Yorke with a substance which he described as "an aromatic diamidine containing no heavy metal." One of the patients was an African male in hospital awaiting operation for hernia, and was diagnosed on the first day of symptoms of sleeping sickness, with high fever, a positive blood, and only two cells per cubic millimetre in the cerebrospinal fluid. The treatment was unsuccessful in all three cases. More recent experiments in 1951 with the latest product, pentamidine, were equally disappointing.

In my opinion pentamidine has no place in the treatment or prophylaxis of trypanosomiasis due to *T. rhodesiense*.—I am, etc.,

St. John's, Antigua. A. J. KEEVILL.

Intravenous Iron

SIR,—I was most interested in Dr. Betty D. Holt's comments (*Journal*, April 11, p. 834) on my paper on intravenous iron (*Journal*, January 3, p. 21). I would be grateful for space to reply to the points raised.

Although I have no idea how many injections are given in England per year, I have no doubt that they must amount to some thousands. Only the severest reactions are usually recorded in the medical press. With present-day preparations, therefore, intravenous iron is a safe procedure if judged on these grounds. I feel, however, that the dangers should not be minimized and that an attitude of complacency is to be deprecated. I am glad, therefore, to see that Dr. Holt is in agreement with this. I consider these reactions to be largely allergic in character. It is well known that tendency to allergy varies in different races. Perhaps racial differences would account for the absence of reaction in her cases.

Finally, in regard to dosage, my early practice was to use a commencing dose of 100 mg. and follow up on alternate days with the same dose, but, since my adverse experience, I now use 25 mg. to 50 mg. at the start. Although I see that Dr. Holt has had no troubles so far with the large doses (100 mg. to 200 mg.) used, I feel that these are too high, unless, of course, the difference in racial sensitivity is a real factor.—I am, etc.,

Romford, Essex. I. M. LIBRACH.

Judet Acrylic Prostheses

SIR,—In recent months a number of Judet acrylic prostheses have had to be removed from patients because of mechanical failure. These failures may be due to one or more of the following factors: the unsuitability of the materials employed, design, manufacturing methods, sterilization procedures, position of insertion of the prosthesis, and fit of the acrylic head in the acetabulum. In collaboration with Dr. Zarek, of the Faculty of Engineering, King's College, University of London, experimental work is being carried out the results of which it is hoped may shed some light on the cause of these failures. The number of cases to which we have access is naturally limited. It would be of the greatest assistance if surgeons and pathologists who remove any prosthesis from a patient (which may or may not be broken), either at operation or necropsy, would be kind enough to send it to me at the Plastics Research Unit, The Institute of Orthopaedics (University of London), Royal National Orthopaedic Hospital, Stanmore, Middlesex. The following information is required: (*a*) a brief pre- and post-operative case history with the actual or estimated weight of the patient (personal details which might identify the patient are not required); (*b*) all radiographs in which the prosthesis can be seen, which will be returned; (*c*) details of method of sterilization and, if possible, whether the prosthesis has been sterilized on a number of occasions; (*d*) the prosthesis.

It is hoped that all those interested in this problem will co-operate, as an investigation of this kind can be of value only if as many as possible of the failures can be investigated.—I am, etc.,

Stanmore, Middx. JOHN T. SCALES.

The Degradation of Flour and Bread

SIR,—In your issue of March 14 last you gave details of the composition of the new white flour as they were given by Dr. Charles Hill, M.P., in answer to a question in Parliament. The figures given are likely to make us think that all will be well with our new white flour, for they appear to show that for every nutritional constituent taken out of the present 80% flour when reduced to a 70–72% extraction one has been replaced in the new 70–72% "restored" flour, except for a slight reduction in protein.

This is far from the truth, because the figures only include three out of the ten or more vitamins of the B-complex group, and only two out of a dozen or so minerals, and do not mention the loss of the roughage (which has its own part to play in our body economy) or the loss of vitamin E. The degradation of our daily bread from about 1870 down to the present time has been a kind of rake's progress. In the space available to me it is only possible to give a very faint picture of it.

Here are a few approximate figures. The ash of whole wheat is 1.53 g. per 100 g.; in 85% extraction it is 0.75; in 80% extraction 0.59; and in a 70%, 0.41.[1] The ash contains the bulk of the minerals, and the reduction of minerals follows largely this reduction—for example, potassium is reduced from 312 to 82 mg. per 100 g. in a 70% flour, and copper from 60 to 18 mg. per 100 g. The vitamins will also show a somewhat similar pattern of degradation—for example, aneurin from 110 to 22 i.u./g., nicotinic acid from 55 to 8.4 μg./g. The three vitamins aneurin, riboflavin, and nicotinic acid are restored in the new flour to the 80% flour level only; and of two minerals, iron is restored to the 80% level of 1.65 mg. per 100 g. but not to the 3.81 mg. per 100 g. of whole meal. Calcium is dealt with differently, in a reinforced manner.

The general result of all this degradation process of whole meal to the new white "restored" flour will be an unbalanced kind of loaf reduced greatly in all its nutritive constituents—calcium, carbohydrate, and, to some extent, protein excepted. Want of balance can cause a nutritional upset as well as the nutritional deficiency diseases caused by individual shortages. It would take a considerable space to describe all these separately, but we do know that they are something that cannot be disregarded. Two will be mentioned.

In pantothenic acid deficiency there are changes in the anatomy and function of the adrenal gland, with degeneration of the cortex; oxidation of fatty acids is also impaired.[2] In pyridoxine deficiency the skin, haemopoietic tissue, and nervous system are adversely affected, producing cheilosis and angular stomatitis and a microcytosis accompanied by polycythaemia and fall in haemoglobin concentration.[3] Generally speaking it is growing tissues that are most affected when pyridoxine is in short supply.

To conclude, I suggest that before any further steps are taken to put the new white flour on the market an inquiry should be held at once by some competent body containing members with experience in deficiency diseases—for example, members of the Medical Research Council, Nutrition Society, Ministry of Health, the B.M.A., and Society of M.O.H.s. The degradation of our daily bread has reached a stage at which there should be a call to halt.—I am, etc.,

Glossop. E. H. M. MILLIGAN.

REFERENCES

[1] McCance, R. A., *et al.* (1945). *Biochem. J.*, **39**, 213.
[2] Hughes, D. E. (1953). *Proc. Nutr. Soc.*, **12**, 83.
[3] Sinclair, H. M. (1953). Ibid., **12**, 94.

Survey of Prescribing in Scotland

SIR,—I have read with interest the article by Professor D. M. Dunlop and Drs. R. S. Inch and J. Paul (*Journal*, March 28, p. 694), but I would like to point out an inaccuracy in their figures which may account for the apparent low mean monthly script rate per 1,000 population in the Highlands and Islands.

For the County of Sutherland, the numbers of scripts given by them in Table III as issued in 1951 include only those dispensed by chemists—I have verified this—and it has apparently been overlooked that five of Sutherland's twelve doctors (not eleven as stated, although in October, 1951, one practice vacancy was in the process of being filled) have dispensing practices with a total of approximately 3,800 patients, which figure should have been deducted from the total number of registered patients. It would not be possible to correct this discrepancy by *adding* the number of scripts dispensed by doctors, as some are paid on a capitation basis and return no scripts except for expensive medicaments.

This applies to all counties in the Highlands and Islands, and the fact that Shetland has by far the lowest monthly script rate per 1,000 is doubtless accounted for by the fact that this county has proportionately the largest number of dispensing doctors.—I am, etc.,

Golspie, Sutherland. IAN D. PENNIE.

The Foley Catheter

SIR,—Mr. G. E. Moloney in his informative contribution (*Journal*, March 28, p. 706) on pelvic evisceration and uretero-colic anastomosis reminds your readers that an anal catheter helps to keep the patient dry during post-operative recumbency.

Where hystero-cystectomy with uretero-colic anastomosis has been accomplished to extinguish an anterior invasion by cervical carcinoma, my gynaecological colleague, Mr. J. A. Chalmers, and I have found a Foley's catheter the perfect conduit for draining the rectal contents during the early period of convalescence. The catheter is inserted above the ano-rectal ring and the bag is inflated, but not sufficiently to cause mucosal pressure-necrosis. A wide-bore instrument will convey away, without soiling the patient's attire, all the faeculent urine and flatus, allowing full liberty of movement, since it is "self-retaining." It is also labour-saving, and the perineal cleanliness reassures the patient when her vitality is at its lowest ebb.

I should like to mention the use of Foley's catheter modified for another operation. When the adenomatous prostate has been removed by any method and the surgeon wishes to leave a urethral catheter in position, he fears that it may be blocked by clot or promote infection. If the bag is removed from the catheter before inserting it into the urethra, and if the eyelet occupies the vacant prostatic capsule, the bladder or the capsule may then be closed after haemostasis and the side tube of the catheter can be used for continuous irrigation. With the patient back in bed it is connected to a reservoir supplying a lotion through a drip tube. The greater tube of the catheter is connected to a receiver, another drip tube of large dimensions intervening so that inflow and outflow coincide. Thus, the two-hourly syringing, so tiresome to the nurse and her patient and often septic, is avoided.

I use initially two flasks of sodium citrate solution and follow this with 1/5,000 flavine in saline. The catheter is removed in 48 hours and the patient usually micturates spontaneously. It is lubricated with penicillin cream. This method of irrigation is to be considered as a modification only of Mr. Wilfrid Adams's "third ureter"—a ureteric catheter introduced into the bladder suprapubically after prostatic enucleation and connected to a reservoir of lotion.

If a Foley catheter could have a second side tube for irrigation, its bag intact, then the triple function could be harnessed to the patient's treatment.—I am, etc.,

Worcester. PAUL HOUGHTON.

Treatment of Perforated Peptic Ulcer

SIR,—I have followed the correspondence on the treatment of perforated peptic ulcer with very great interest, but I am not quite sure that the routine practice of simple closure is obsolete, even though this may entail a second operation later on. I have performed personally, or through my assistants, 673 closures with only one death.

Since I standardized my treatment it has not varied. This consists, immediately the diagnosis is made, in gastric aspiration and a saline drip, and then, after the operation, further aspiration and the continuance of the intravenous saline for at least another 48 hours. I must confess that the majority of these cases were Service people, which means that there was no delay in their admission to hospital and that they were in good condition otherwise. But not a few were performed on African natives before the 1939–45 war. The

one death occurred in a young soldier who had perforated 48 hours before admission: he died a week after the operation and, regrettably, no necropsy was allowed.—I am, etc.,

Epsom, Surrey. S. M. VASSALLO.

SIR,—Mr. Hermon Taylor (*Journal*, April 4, p. 781), in discussing the conservative treatment of perforated ulcers, says, "Clearly the method of gastric aspiration can achieve all that can be obtained by the method of surgical closure, but with the not inconsiderable advantages of avoiding an operation." He further states that modern developments have made simple closure of perforations obsolete. To my mind, operation has several possible advantages: (1) fluid can be sucked out of the subphrenic spaces; (2) the size and situation of the ulcer can be assessed; (3) the possibility of malignant change can be largely excluded; and (4) appropriate treatment can be given if the diagnosis proves to be wrong—e.g., perforated cholecystitis, appendicitis with general peritonitis, pancreatitis, or even small-bowel obstruction.

Continuous aspiration has its disadvantages. It is usually necessary for four to five days, and entails intravenous saline with all its dangers and complications. A very high proportion of cases treated by operation only need gastric suction for about 36 hours. A rectal drip is then quite adequate to prevent dehydration.

Surely the discomforts and dangers of operation have been exaggerated during recent years. It has been my practice to combine local and light general anaesthetics, which give complete relaxation without any interference with chest or diaphragmatic movements. The patient usually wakes up almost free from pain. I have personal experience of 385 operations, and I think that a patient who cannot stand this line of treatment is most unlikely to recover from any other.—I am, etc.,

Farnham, Surrey. STANLEY C. RAW.

Research in General Practice

SIR,—Professor Robert Platt's address (*Journal*, March 14, p. 577) was indeed stimulating, but those who try, however unpretentiously, to carry his ideas into practice do not always find that things go very smoothly. Some years ago I was taunted by a patient that British medicine lagged behind the Soviet variety inasmuch as Russian doctors were completely relieving the pangs of childbirth by injections of vitamin B. This information had been gleaned from a Soviet propaganda publication which had considerable circulation in this country. I wrote immediately to a firm which is generous in the matter of circulars and samples, and is prominent as a manufacturer of vitamin products. I suggested that the matter might be very quickly tested by the issue to a sufficient number of general practitioners of enough vitamin B to be used in their cases, on condition that reports were sent of the results. The firm's medical adviser pooh-poohed the whole project.

On another occasion I wrote to the *Journal* on the subject of the long-term results of electric shock treatment in mental illness, because I felt that general practitioners would have more reliable views on the subject than those held by the more enthusiastic psychiatrists. If my memory serves me correctly there was no reaction, good, bad, or indifferent, from my colleagues.—I am, etc.,

Launceston. DONALD M. O'CONNOR.

Chloroform for Bronchography in Children

SIR,—Mr. Leslie J. Temple and Dr. T. Cecil Gray, in their letter (*Journal*, April 18, p. 883) commenting on our article on bronchography in children (*Journal*, March 14, p. 601), state that it implies that the child may suffer from hypoxia during the use of our technique. This is certainly not so. We attain rapidly a short, deep anaesthesia and at all times the child is well oxygenated. We do not suggest that chloroform should be used by the inexperienced, but we think that explosive agents are better avoided in the *x*-ray room.

As regards the airway, it may be difficult to prevent obstruction without it in some of those children with enlarged tonsils and adenoids. Finally, an important difference between our technique and Gray and Temple's, not mentioned in their letter, is that we do not "drown" our patients with lipiodol, as we feel that in bronchiectasis there is enough foreign material in the bronchi without adding to it more than the minimum necessary.—We are, etc.,

MARGARET I. GRIFFITHS.
Manchester. T. D. CULBERT.

SIR,—Having used the method of anaesthesia for bronchography in children described by Mr. Leslie J. Temple and Dr. T. Cecil Gray (*Journal*, April 18, p. 883) since I was first taught it by Dr. John Halton some five years ago, I can only agree with all the authors' remarks concerning the method.

Being worried about the possibility of explosion, I too tried chloroform and other agents, but soon realized, fortunately at the cost only of minutes of acute anxiety on more than one occasion, that as deep anaesthesia is necessary it is most safely produced by ether. I feel convinced that explosions as a result of ignition of ether vapour by *x*-ray equipment have been much rarer than fatalities from the use of chloroform, and would join Mr. Temple and Dr. Gray in pointing out the dangers of using chloroform where some degree of hypoxia is to be expected as a result of deep anaesthesia and the introduction of oil into a diseased respiratory system.—I am, etc.,

Manchester. TOM DINSDALE.

Antihistamines and Asthma

SIR,—Drs. A. W. Frankland and R. H. Gorrill (*Journal*, April 4, p. 761) ought to be congratulated on the skill with which they have refuted the assumption that antihistamine treatment of hay-fever causes asthma. Their further conclusion that antihistamines do not improve asthma is hardly justified by their experiments. They have given mepyramine, apparently in four separate daily doses of 100 mg., or another equivalent antihistamine, and have not seen any benefit from it. Nor have I. Antihistamines influence asthma only if a much larger dose is given than that effective in allergic rhinitis. There is ample evidence for their efficiency,[1 2] but I have never seen a beneficial effect with less than a single dose of 300 mg. of mepyramine. An amount of 100 mg. cannot be expected to influence asthma, just as one would not expect one minim of adrenaline to influence it. It would appear essential that in therapeutic trials, controlled or uncontrolled, the doses used are not subthreshold ones, as in this case.

The difficulty with antihistamines in asthma is that the large doses required often have side-effects which make their use impracticable during the day. They are best used in single doses at bedtime, when they may secure an asthma-free night. The use of one single dose in 24 hours also avoids the development of tolerance, which easily occurs with multiple doses.[3]—I am, etc.,

London, W.C.1. H. HERXHEIMER.

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Television and the Patient

SIR,—I should like to endorse very strongly the opinion expressed by Dr. T. Hughes (*Journal*, April 18, p. 884) in the letter under the heading "Television and the Patient." In general, television programmes on medical subjects seem calculated to foster in the minds of ordinary people the

deplorable idea—already far too prevalent—that the attitude of the medical profession can be expressed as, "It doesn't really matter how you live: modern medical science is so wonderful that you can be made fit whatever happens—if you are properly treated." The view that it is the business of the State, through its "Health" Service, to make and keep everyone healthy is thus still further encouraged instead of the true view that it is the duty and privilege of each individual to think and live in such a way as to attain the greatest possible degree of mental and physical efficiency.

Soon after I had a television receiver installed in my home (about two years ago) I was so impressed by the possibilities of television as an educational medium that I summoned up courage to write to the B.B.C. to suggest, humbly, that it might be a very good thing if a small amount of time (perhaps 20 or 30 minutes once a month) could be devoted to a health education series in which a plainly worded and interestingly illustrated exposition of relevant biological facts could be given, coupled with hints on "keeping fit" based on these facts. After some time I received a letter in reply which said that I should be glad to know that the sort of programme I advocated was being sent out from time to time, and went on to instance the very sort of thing that Dr. Hughes has referred to. I wrote again and tried to explain as carefully as I could the difference between that kind of programme and the educational programmes that I felt could be so beneficial, but again I got a reply which seemed to indicate a complete failure to see my meaning, and I am afraid I gave up the struggle as hopeless.

Would it be possible for representations to be made to the B.B.C. on this matter?—I am, etc.,

London, N.W.3. A. DALBY.

SIR,—As one responsible for the section on anaesthetics in the "Pain" programme referred to (*Journal*, April 18, p. 884), I think that Dr. Trevor Hughes's letter has served a useful purpose in attracting attention to the subject in the daily press. The contribution of anaesthetics to the advancement of surgery is now freely recognized in the medical profession, and the consumers—the public—are entitled to information upon it. From the comments I have heard from time to time from lay members of the public, it is clear that interest in such matters springs from healthy intelligence and but rarely from morbid curiosity.

Whatever the merits of the "rag and bottle" administration of anaesthetics may be, to many people experience of it is a distasteful memory. It is fair that the public should know that in experienced hands more pleasant methods of anaesthesia are available to all in this country—as they should be under the Health Service. Television provides a useful medium for extension of this knowledge. Can Dr. Hughes suggest a better medium, or would he prefer his patients to be kept in ignorance?—I am, etc.,

London, W.1. I. W. MAGILL.

Polypharmacy

SIR,—Dr. A. T. Mennie (*Journal*, April 18, p. 887) overstates his case. While multiple deficiencies may be common in anaemia—though which is cause and which is effect may be hard to say—it is still a fact that the common so-called "nutritional hypochromic anaemia" can be treated adequately with iron alone. Even when combinations of therapeutic substances produce a more rapid rise in haemoglobin, speed of cure alone is seldom important.

There are those whose hypochromic anaemia responds inadequately or not at all to iron. After investigations have excluded haemorrhagic or other organic causes there may be a place for treatment with multiple agents, the nature and dosage of which should depend upon each patient's needs and not merely be determined rigidly by the contents of a capsule.—I am, etc.,

London, N.W.6. J. I. E. HOFFMAN.

POINTS FROM LETTERS

Counting High Pulse Rates

Dr. R. J. K. BROWN (London, S.E.24) writes: Dr. E. Montuschi (*Journal*, April 4, p. 781) mentions a technique for counting high pulse rates. May I describe another which is equally applicable to both high and low pulse rates? . . . The number of beats are counted in three consecutive five-second periods: the highest and lowest figures so obtained are then multiplied by 12. For example, if these figures were 6 and 7, one could say the pulse rate was swinging between 72 and 84 (with a mean of 78). I have found this method particularly useful in paediatric practice.

Drunk in Charge

Dr. C. RUTTER (London, E.6) writes: I was interested to read Dr. A. E. M. Hartley's article (*Journal*, March 28, p. 735) on "drunk in charge." I would suggest, however, that the examination should take place immediately on arrival, before the essential questions are asked. The medical history might be long and take time to obtain in full, thus giving the person being examined time to sober up.

Research in General Practice

Mr. A. P. BERTWISTLE (Birmingham) writes: In Professor Robert Platt's admirable paper on the above (*Journal*, March 14, p. 577) he instances the experiment of cleaning the teeth on one side to find out whether the tooth-brush prevented caries. There is an important snag—the subject must sleep on his back. Most of us sleep on the left side, with the result that tartar forms more abundantly on this side, and this may have its repercussion on caries.

Comfort in Air Travel

Dr. FLORENCE ADAM THOMSON (Ipoh, Malaya) writes: I should like to refer to Part I of Sir Harold Whittingham's refresher course article on air travel (*Journal*, March 7, p. 556). I realize that considerable thought has been given to the design of aircraft seating so that passengers may have reasonable comfort in a confined space. Has it been brought to the notice of B.O.A.C. that, despite this, most passengers are quite unable to rest in comfort in the position allowed, and sleep is quite impossible except in very short snatches? I and many friends of average stature have found that after a journey there is such severe oedema of feet and legs that to walk or work in comfort is impossible for several days. Were a little extra space given on the longer runs, with tilted seating and leg rests similar to that on some American lines, passengers could rest and arrive refreshed even when no night stops are made.

Slipped Disk

Dr. HUGH GARLAND (Leeds, 1) writes: I am not quite sure when and where the term "slipped disk" was coined, but it has now passed into common usage and indeed it has become one of the stock jokes of the comedian. It is a most improper term, carrying the implication that the whole disk has slipped in some direction in relation to the vertebrae above and below, and there is a popular corollary that, having slipped out, the disk is capable of slipping back. As far as I know such a pathological state has never been seen by the human eye. I think it is our duty to discourage this terminology, and I was perturbed to see the unhappy term used in the *Journal* ("Any Questions?" March 7, p. 575). Syndromes resulting from damage to intervertebral disks have been diagnosed with increasing frequency over the past 15 years, so that to-day the disk lesion is well known to the public. The main change in the disk is one of protrusion, usually of a very localized kind, and to which the terms "herniation" or "protrusion" are very properly applied—but not "slipped."

Chlorophyll and Asparagus

Dr. JOHN DICKINSON (London, W.C.1) writes: Dr. John C. Brocklehurst (*Journal*, March 7, p. 541) has suggested that doctors should experiment on themselves with asparagus, to determine whether the smell of their urine is reduced by chlorophyll. Since supplies of this drug are expensive there is a danger that the experiment may be invalid through shortage of either doctors or asparagus, or both. Might I suggest that the Medical Research Council should send regular quantities of asparagus to two large groups of doctors? Half of these could then receive chlorophyll and half act as controls. If the experiment was conducted on a sufficiently large scale, statistically significant results could be of the greatest value to the public. Clearly, several weeks or even months of patient trial would be necessary; but nevertheless I am pleased to offer myself as a volunteer—preferably in the control group.

Obituary

H. S. PENDLEBURY, M.B., F.R.C.S.

Mr. H. S. Pendlebury, at one time a surgeon on the staff of St. George's Hospital, died on April 21 at his home at Malvern.

Herbert Stringfellow Pendlebury was the son of John Pendlebury, J.P., of Wigan, and was born there in 1870. He won a scholarship at Pembroke College, Cambridge, and took a first in both parts of the Natural Sciences Tripos. His small stature handicapped him for some games, but he played for his university at hockey. From Cambridge he entered the medical school of St. George's Hospital with a scholarship, qualified in 1896, took the F.R.C.S. in 1897, and graduated M.B., B.Ch. in 1898. In turn he served his hospital as house-surgeon, house-physician, surgical registrar, assistant surgeon, surgeon, and lecturer in surgery. He was also surgeon for many years to the Royal Waterloo Hospital, remaining on the consultant staff there until his death. When Pendlebury was training himself in surgery, Listerian principles had for some years already won their victory; but there were still a good many of the older men in the profession who thought they comprehended them, but in fact did not completely do so. It thus happened that in the 'nineties a group of eager and progressive young surgeons in London (and probably the same was done elsewhere) found themselves producing results which surpassed those obtained by some of their seniors. The expansion of abdominal surgery, set on foot very largely by Sir Frederick Treves, gave them a further opportunity; and Pendlebury was one of those who profited by all this to obtain glittering success in practice at a comparatively early age. He was a deft, rapid, and scrupulously careful operator and a very good teacher. One of his foibles was a somewhat unusual view of the meaning of punctuality, on which he was rightly very insistent: he maintained that to be punctual you must be five minutes early for your assignment, and could be almost bitter in his reproaches of any subordinate who failed to act up to this. For him an operation list commencing at 2 p.m. meant that the first patient must be in the theatre, anaesthetized, and with all the necessary ritual completed, so that the skin incision could be made as the clock struck the hour.

Pendlebury was a man of very great energy and organizing ability, which he employed in the promotion of two ventures, novel at the time, but now accepted as part of the natural order of things. The Royal Society of Medicine was one of these, founded in 1907 by the amalgamation of eighteen societies representing, for the most part, specialties in medicine and surgery. When this federation was accomplished, he was the Society's honorary secretary for some years—the most difficult ones, of course—and honorary treasurer for some years thereafter. In both capacities he served the profession extremely well. The next organization which he helped to promote was that of the Association of Surgeons of Great Britain and Ireland in 1920, in which Lord Moynihan was keenly interested. Here again his organizing ability and enthusiasm were valuable assets.

During the first world war Pendlebury served in the R.A.M.C., being attached to the 4th London General Hospital. He contributed a number of case reports to medical journals, and was the author of two chapters in Latham and English's *System of Treatment*. Besides being a member of the Court of Examiners of the Conjoint Board, he examined in surgery for the University of Cambridge and the Society of Apothecaries.

Pendlebury married first Lilian Dorothea, daughter of the late Sir T. L. Devitt: she died in 1921, leaving as issue Mr. J. O. S. Pendlebury, who, after gaining an athletic Blue at Cambridge, was rapidly making a name for himself in archaeology, and was killed in Crete in 1941 during the German invasion of the island. He married again in 1925, his second wife being a daughter of Mr. Richard Webb. He was interested, among many other things, in education, and gave £100 to Epsom College to found a prize for Greek studies there.

ALEXANDER MITCHELL, M.B., Ch.M.

Mr. Alexander Mitchell, well known as an orthopaedic surgeon in the north-east of Scotland, died in Aberdeen on April 16, aged 72. Although he had been in indifferent health for some months, he had two days previously, with characteristic sense of duty, insisted on travelling from his home at Old Rayne to attend a hospital board meeting in Aberdeen, and it was while acting as chairman there that he was stricken with fatal illness. He faced death with the same spirit and fortitude that he displayed throughout his life, his thought being not for himself but for the trouble he might be causing others.

Alexander Mitchell was educated at Robert Gordon's College and Aberdeen University, graduating M.A. in 1901, M.B., Ch.B. in 1905, and Ch.M. in 1907. After a few years in general practice he devoted himself entirely to surgery, mainly at the Royal Aberdeen Hospital for Sick Children and Aberdeen Royal Infirmary. He served as a captain in the R.A.M.C. in the first world war, and at its conclusion became senior surgeon at the Children's Hospital, holding that position until he took charge of the orthopaedic unit at the Royal Infirmary in 1936. He organized the orthopaedic services of the north-east of Scotland and was prominent in the councils of the British Orthopaedic Associations, of which he became vice-president. He was also an external examiner in surgery to the University of Edinburgh. When he retired from active surgical practice his services were eagerly sought in hospital management and he was elected chairman of the Special Hospitals Board a year ago. Into this work he threw himself heart and soul, welcoming an opportunity for service in a field where his intimate knowledge of medical practice, both outside and inside hospital, would be of value to the community and the profession. In 1942 he was made a J.P. for the county of Aberdeen.

To every aspect of his work "Sandy" Mitchell brought a driving force and a devotion beyond praise. Chairman of the Aberdeen Division of the B.M.A. in 1929, he was elected president of the Orthopaedics and Fractures Section at the Annual Meeting in Aberdeen in 1939. He served the profession that he loved without stint and without calculation, disregarding his own lameness and labouring day and night for the sick and especially for the crippled. His main attributes were a forthright honesty that informed his every thought and action, a love of his fellow men, outstanding magnanimity, and high courage. As patients flocked to him for relief, so did his colleagues seek his advice and help. He was laid to rest at Rayne, in the land of his fathers that he knew so well and loved so much, and the whole community sorrowed at the passing of a great-hearted and beloved son.

He married in 1913 Ada, daughter of the late Dr. Greig, of Fyvie. She predeceased him, leaving two sons, one of them a major in the R.A.M.C., and a daughter. To them and to his second wife, Alice, daughter of the late Dr. David Rorie, we extend our deepest sympathy.—S. G. D.

F. W. EDRIDGE-GREEN, C.B.E., M.D., F.R.C.S.

Mr. F. W. Edridge-Green, whose work on the testing of colour vision won him international fame, died at Worthing on April 17. He was 89 years of age.

Frederick William Edridge-Green, whose family were well known in the Potteries as the makers of the famous Crown Staffordshire ware, was born in London on December 14, 1863. He received his medical education at Durham University and St. Bartholomew's Hospital, where he won a scholarship and several prizes. He graduated M.B., B.S. in 1887 and proceeded M.D. with the award of a gold medal two years later. He became F.R.C.S. in 1892. After holding the posts of resident surgical assistant at the Newcastle-upon-Tyne Infirmary and assistant medical officer at Northumberland House Asylum he became medical superintendent of Hendon Grove Asylum. At this stage of his career he had two diverse interests—the functions of the mind, especially memory (on which he published several papers), and colour vision, about which he contributed an article to this *Journal* as early as 1889. But gradually the study of the physiology of vision became his overriding enthusiasm, and he continued his researches while retaining his post at Hendon Grove Asylum. Though some of his ideas were strongly disputed by other experts, his devotion to the cause of medical research was wholly admirable.

In those days official recognition was given to the Holmgren wool test as the method of testing colour vision, and Edridge-Green was one of the first to point out the disadvantages of this method, one of his papers on the subject appearing in the *Lancet* in 1900. Although he was made a member of the International Code of Signals Committee, his views were not at first accepted, but after the publication of his treatise on *Colour Blindness and Colour Perception* in 1909 other authorities began to confirm his work, which also received the support of a committee of the British Association. Eventually, soon after the beginning of the first world war, the colour-perception lantern devised by Edridge-Green was brought into official use for colour-vision testing by the Royal Navy, the Board of Trade, the railways, and other bodies throughout the world. The bead test, used by National Service boards, was also his invention. The many honours and distinctions which later came his way testified to the importance of his work. In 1920 he was appointed C.B.E. and also made adviser to the Board of Trade, and, later, to the Ministry of Transport. At the College of Surgeons, having been prosector at an early stage in his career, he was Hunterian Professor in 1911 and the Arris and Gale lecturer in 1920. He was also a Beit Memorial Research Fellow and worked for a time at Cambridge. In 1930 he was president of honour at the annual meeting of the Ophthalmological Society of Paris, and six years later he was awarded the Thomas Gray Memorial Prize for his invention of the colour-perception lantern. A distinction which pleased him was the presidency of the Durham Medical Graduates Association.

Much of Edridge-Green's professional work was done as ophthalmic surgeon to the London Pensions Board, and he was also chairman of the Ophthalmic Board of the Central London Recruiting Boards for National Service. The author of numerous papers in English and foreign scientific journals, he published a book entitled *The Physiology of Vision* in 1920 and wrote the section on colour vision and colour blindness in the *Encyclopaedia Britannica* (1922). He was an able mathematician and a skilful player of chess and bridge. Some details of his life and early struggles are contained in his book *Science and Pseudo-science*, published in 1933. His interest in the physiology of vision continued right up to his death, and only a few weeks ago he paid one of his usual visits of inspection to the factory at Hove where the colour-perception lanterns are manufactured.

In 1893 Edridge-Green married Minnie Jane, daughter of Henry Hicks, M.D., F.R.S. She died in 1901. They had two sons, one of whom died in childhood; the other, who served in the first world war, died shortly after the armistice.

JOHN GUY, M.D., F.R.C.P.Ed., F.R.F.P.S., D.P.H.

Dr. John Guy, who died at his home at Aberlady, East Lothian, on April 11 at the age of 79, was medical officer of health for Edinburgh from 1930 to 1938. He had been in the service of Edinburgh Corporation for 25 years, and was the fourth medical officer of health for the city.

John Guy was born at Saltcoats, Ayrshire, on October 4, 1873, and was educated at the University of Glasgow, where he graduated M.B., C.M. in 1894, proceeding to the M.D. six years later. He took the Cambridge D.P.H. in 1899, and he was elected F.R.F.P.S. in 1911 and F.R.C.P.Ed. in 1917. After graduation Dr. Guy held posts in Poor Law hospitals in Bradford and Leeds before becoming medical superintendent of the Bridge of Weir Sanatorium, where he stayed for seven years. Thereafter he was for a short time tuberculosis officer for Gloucestershire, the first to hold the post, before accepting a similar position at Edinburgh in 1913, an appointment made jointly by the corporation and the burgh insurance committee in accordance with the provisions relating to tuberculosis in the National Insurance Act of 1911.

When he took office as medical officer of health for Edinburgh the health services were being unified under the Local Government (Scotland) Act of 1929. At that period public health administration in the city was limited to the control of infectious diseases, environmental and veterinary services, an infectious diseases hospital, a sanatorium and farm colony, and specialist departments for tuberculosis, venereal diseases, and maternity and child welfare. Under the Act the health functions previously carried out by the parish council and the local board of control were transferred to the public health department, including the conduct of two general hospitals for the sick poor, a mental hospital with over 1,000 beds, and a newly inaugurated institution of 500 beds for mental defectives, and to these new duties was added also the task of supervising the health of 60,000 schoolchildren. The changes represented the largest single addition to the burdens of a medical officer of health, and while they called for careful assimilation they also provided an opportunity for improved co-ordination. By 1938, when he retired, Dr. Guy had succeeded in establishing a chain of three general hospitals in which the treatment of the patients was directed by the medical staff of the University of Edinburgh, whose professors were the heads of the medical, surgi-

cal, and maternity and child life units. The association of "town and gown" raised the prestige of the hospitals and earned the warm approval of the citizens. When war broke out in 1939 the three hospitals, with many more beds and new equipment, became a valuable part of the country's emergency medical service. Dr. Guy had a special regard for the school health service, and this was reflected in his introduction of more frequent medical inspections and an increased scale of specialist treatment.

Dr. Guy was a former lecturer on public health in the University of Edinburgh, on tuberculosis at the School of Medicine of the Royal Colleges, and on hygiene in the School of Social Study at Edinburgh. Together with the late Dr. G. J. I. Linklater, he was the author of a widely used textbook on *Hygiene for Nurses*. A man of deep religious principles, Dr. Guy was associated with various benevolent societies in Edinburgh. He had a keen appreciation of music, and another of his interests was farming. He leaves a widow, three sons, and a daughter.

C. J. McSWEENEY, M.D., F.R.C.P.I., D.P.H.

We record with regret the death on April 17 of Dr. C. J. McSweeney, medical superintendent of the Cork Street Fever Hospital, Dublin.

Born at Cork in 1899, Christopher Joseph McSweeney was educated at the Christian Brothers' College and at University College, Cork, where his father, Mr. E. P. McSweeney, was a member of the staff. A brilliant student, he won a number of scholarships and prizes and graduated M.B., Ch.B., with first-class honours, in 1921. Nine years later he proceeded to the M.D. After graduation he held the appointment of extern assistant to the Rotunda Hospital, Dublin. In 1925 he took the D.P.H. and became assistant medical officer of health at Cardiff. Two years later he was promoted to be deputy to the then medical officer of health, Dr. R. M. F. Picken. Among his other duties Dr. McSweeney was in charge of the Cardiff Isolation Hospital, and he was also appointed lecturer in infectious diseases and associate examiner for the Welsh National School of Medicine.

In 1934 he returned to Ireland to become medical superintendent of the Cork Street Fever Hospital, Dublin, a post which carried with it lectureships in infectious diseases in the Dublin medical schools together with the appointment of consultant in infectious diseases for the city. In the previous year he was elected a Member of the Royal College of Physicians of Ireland, being admitted a Fellow three years later. From 1937 to 1939 he was a Censor of the College. In addition to the appointment at the Cork Street Hospital, he was deputy professor of preventive medicine at Trinity College and consulting physician in fevers to the National Children's Hospital and the Fairy Hill Open Air Hospital. He was also an examiner for nursing councils, both in Northern Ireland and in Eire, and for the D.P.H. of the Dublin medical schools.

Dr. McSweeney was the author of many important papers about infectious diseases, and his most recent book, *The Clinical Approach to Fevers*, appeared only last month. A paper which he wrote in 1941 was entitled "A Public Health Programme for Eire"; this was published in the *Irish Journal of Medical Science*. He married Miss Evelyn H. Donegan in 1923, and she survives him, together with one son.

We are indebted to Dr. R. M. F. PICKEN for the following appreciation: During the first half of the present century, when infectious diseases were still prevalent and epidemics fairly frequent, and while the new personal health services were developing quickly, the most acceptable members of public health departments were those who could turn their minds to new problems or sudden emergencies and cope with them without close supervision. McSweeney was pre-eminently of this type, a type which the public health service has found it hard to retain because of the poor material prospects. When he came to the public health department of Cardiff he was still a very young practitioner. He soon showed that he had this sort of initiative as well as unusual ability and assiduity. A problem became all-absorbing to him until he had found some practical channel for its issue. Thus he undertook from the beginning the management and clinical supervision of an institution earmarked for early cardiac rheumatism in children until it was a going concern. When variola minor broke out in epidemic form in South Wales he threw himself into its diagnosis and control so vigorously that his help was sought in a neighbouring urban district, where his energy and diagnostic skill were instrumental in bringing it quickly to an end. In his latter years in Cardiff he was both deputy medical officer of health and medical superintendent of the isolation hospital and lecturer in infectious diseases in the Medical School, arduous tasks which he fulfilled with signal success.

McSweeney had a delightful temperament, warm, kindly, and friendly to all those in any station of life with whom he came in contact. He had a keen sense of humour and a ready wit. I think he was happy in South Wales and appreciated the qualities of those natives of this other island with whom he worked. We, of course, saw less of him after he became medical superintendent of Cork Street Hospital, Dublin, but we watched with interest and appreciation his development as a clinician and a teacher, and judged from his writings and from fairly frequent personal contacts that he must have had a great and beneficial influence on his younger colleagues and his students. He had just taken up residence in a new hospital which he had been planning for years and which was about to be opened. We mourn his untimely death and extend our heartfelt sympathy to his widow, who was also at one time a teacher in the Medical School in Cardiff, and to his young son.

EUGEN POLLAK, M.D.

Dr. Eugen Pollak, lecturer in neuropathology at Manchester University, died at the Manchester Royal Infirmary on April 9, aged 62. A Viennese by birth and a widower for many years, Pollak was a refugee from the Nazis, arriving in Oxford soon after the rape of Austria. In the Radcliffe Infirmary he found a temporary home in the company of del Río Hortega and Gustav Steiner, with whom he worked in the department of the ever-hospitable Hugh Cairns. Pollak never doubted the outcome of the war, but he must have thought his return to Austria unlikely. In Oxford he was cheerful, courageous, and prepared to bide his time. He longed for work, but demanded nothing; what he was given to do he did willingly, and he never complained. Del Río Hortega was already installed as Oxford's neuropathologist. He and Pollak were as different in personality as they were in training, and with the added difficulty of language there was little contact between them: the Spaniard looked with suspicion on the Austrian whose scientific upbringing made it difficult for him to recognize the concept of the mesoglia. Pollak's opportunity was to come soon. In 1939 he was invited by Sir Geoffrey Jefferson to organize a department of neuropathology in the university service of neurosurgery in Manchester. The acceptance of this offer

he never had cause to regret, and from his letters it was clear that he was happy there—as happy indeed as any Viennese could be in exile. Before he came to England the vivacious Pollak was a prolific writer and was well known for his contributions on tuberous sclerosis, Wilson's disease, and the neuroglia. His publications, based on his work in the departments of Professors Obersteiner and Marburg, mostly appeared in the *Arbeiten aus dem Neurologischen Institut* and in the *Jahrbücher für Psychiatrie und Neurologie*. He was the author of the section on the anatomy of the spinal cord, medulla, and pons in Bumke and Foerster's *Handbuch der Neurologie*. The forced change of country, however, and the building up of a new department, and latterly the threat of ill-health, disturbed the lines of research on which he had been working, and he never really regained the threads. Dr. Pollak's only daughter lives in Vancouver.

W. H. McM. writes: We remember Eugen Pollak as a hearty man, upright in bearing, dark, clean-shaven, and with an excellent sense of humour. Always confident and at times dogmatic, he could be counted upon to enliven equally a discussion on the political future of Europe or on the functions of the neuroglia. In moments off duty we knew him as a *bon viveur*, with an extensive and practical knowledge of the chef's art, and a lover of music. In the early days over here he knew little English, but he was always resourceful. Once, with an obvious effort of will, he declined a second helping of a rich entremet, pointing to his waist-line and explaining, "For me, please, it is too 'periculous.'" Had he been a younger man Pollak might have done more original work in the kindly environment of Manchester, for he had both originality of outlook and great technical skill. As it was he built up a valuable collection of material which will serve others in good stead. Beneath a brave and cheerful façade Pollak was a lonely man who grieved over the fate of his country and also the death of his sister, another victim of racial intolerance.

We record with regret the death of Dr. ALBERT COLEMAN at his home at Croydon on April 13, the day after his 54th birthday, after a long and trying illness. Albert Coleman was born at Manchester and educated at Manchester Grammar School. In 1917 he was awarded an open classical exhibition at Wadham College, Oxford, but the war prevented him from continuing with his classical education. After active service as a combatant officer with the 2nd Battalion the Manchester Regiment, he entered Manchester University, where in 1923 he gained the prize in clinical medicine and graduated M.B., Ch.B. In 1929 he became a Member of the Royal College of Physicians of London. After graduation he held the appointments of house-physician and house-surgeon at Manchester Royal Infirmary and of resident medical officer at Ancoats General Hospital. In 1926 he was appointed a house-physician at the Brompton Hospital, where he was later resident medical officer for two years. In 1932 Dr. Coleman settled in practice at Croydon, where he rapidly developed a large practice and established a reputation for his sound clinical judgment. He was also a skilful anaesthetist, and in 1942 obtained the Diploma in Anaesthetics of the English Royal Colleges. He was appointed an anaesthetist to Croydon General Hospital in 1936 and was also on the staff of the Bethlem Royal Hospital, the Seamen's Hospital, Greenwich, and Warlingham Park Hospital. In 1946–7 he was chairman of the Croydon Division of the British Medical Association, a position he held with distinction. He held definite opinions about the advent of the National Health Service and its impact on the relationship between doctor and patient, and he also had emphatic views about the committee-bound structures he felt had been erected, but he had a kindly and happy disposition and made no enemies. His recreations were shooting and photography, in which he took great enjoyment and possessed considerable skill. Some of his colour photography won him international repute. The sincere sympathy of his colleagues, friends, and patients will be extended to his widow and two daughters.

We are indebted to Dr. P. POSFORD for the following appreciation: The death of Dr. Albert Coleman has left a sad gap in the ranks of the medical profession. He was a fine doctor, much respected for his skill and professional judgment by a wide circle of doctors in and around the Croydon area, and, while he took great pains to apply the latest advances for the cure of disease, he never forgot that the patient was a person first of all. He was the kindest of men, always gentle, and quick to help those in trouble, and he had a keen and subtle sense of humour. It was always a great pleasure to be with him. It was my privilege to attend him in his last long illness, and, while he bore physical pain with great and quiet fortitude, he derived his main strength to face up to the reality of death from his firm faith in God, which was of more value to him than the medicine of his doctors.

Medical Notes in Parliament

Health Visitors

Mr. SOMERVILLE HASTINGS asked the Minister of Health on April 20 how many health visitors per 10,000 of the population were employed in England and Wales, which were the highest and lowest ratios, and in which county or county borough these were found.

Miss PAT HORNSBY-SMITH informed him that on December 31, 1951, the number of health visitors employed by local health authorities (two part-time being taken as roughly equal to one whole-time) was 0.9 per 10,000 of the population. The highest and lowest ratios were 3.5 in the county of Radnor and 0.16 in the Soke of Peterborough.

Health Service Inquiry

Miss PAT HORNSBY-SMITH, Parliamentary Secretary to the Ministry of Health, stated on April 23, in reply to Mr. A. Blenkinsop, that the Minister hoped to be able in a few days to give further information about the composition of the committee of inquiry into the National Health Service.

Dr. BARNET STROSS asked to what extent the terms of reference of the committee included powers to consider salaries paid to medical and non-medical staff, and the economies that might be effected by employing consultants on a full-time basis only.

Miss HORNSBY-SMITH replied that the Minister would certainly not expect the committee to deal with actual rates of pay. For the rest, the Secretary of State for Scotland and the Minister of Health were anxious not to hamper the committee in their work by seeking to restrict their field of inquiry.

Poliomyelitis Research

Mr. JOHN T. HALL on April 23 asked the Minister of Health if he was aware that constant appeals were being made for funds on behalf of the National Fund for Poliomyelitis Research, what steps were being taken to combat this disease, and whether he would consider increasing Government assistance to facilitate the work of finding a cure.

Miss PAT HORNSBY-SMITH replied that the Minister was aware of these appeals, and welcomed help which the fund might be able to give to supplement research. Treatment was provided within the National Health Service mainly by the hospitals, in an increasing number of which special units were being provided. An extensive programme of research was being sponsored by the Medical Research Council, and was not restricted by lack of funds.

Tobacco and Cancer

Mr. FREDERICK WILLEY asked the Minister of Health on April 23 what further research he was undertaking consequent upon the report of his chief medical officer that suspicion continued to be thrown on tobacco, especially heavy cigarette-smoking, for the disturbing increase in male mortality from cancer.

Miss PAT HORNSBY-SMITH replied that this matter had been referred to the Standing Advisory Committee on Cancer and Radiotherapy, and the Minister was awaiting their advice. Meanwhile the existing research would be continued.

Litigation Against Doctors

Air Commodore A. V. HARVEY on April 23 asked the Minister of Health what steps he was taking to safeguard doctors from litigation resulting from their work in the Health Scheme.

Miss PAT HORNSBY-SMITH replied that officers of the department were discussing with representatives of the profession the relations, financial and other, between hospital authorities and their medical staffs when legal actions were brought against either or both.

Food Hygiene

Mr. G. H. OLIVER on April 23 asked the Minister of Health what steps were taken to ascertain whether persons employed in the preparing, cooking, and serving of food in hotels, restaurants, and road-side cafés were free from infectious diseases such as tuberculosis.

Miss PAT HORNSBY-SMITH answered that there was no general power to require the persons concerned to be medically examined for this purpose, and the Minister was advised that the present state of our knowledge did not suggest that such a power would be justifiable as a means of preventing the spread of infection.

Medico-Legal

DAMAGES AGAINST HOSPITAL

Damages of £4,000 were awarded by Mr. Justice Gerrard on April 22 to Mr. R. J. Crawford, aged 52, against Charing Cross Hospital. Mr. Crawford alleged that damage to his left arm sustained during an operation was caused by negligence. The defendants, the board of governors, denied liability. The judge ordered a stay of execution pending appeal.

In view of the concern which cases of alleged negligence have recently been causing the medical profession, it is to be hoped that it will be found possible to take the case to appeal.

The operation, which was performed at Charing Cross Hospital on July 7, 1950, was on the bladder, and the patient was placed in the Trendelenburg position, with shoulder rests. His left arm was abducted and a vein in it used for blood transfusion. After the operation the arm was found to be partially paralysed. His right arm was already paralysed from an attack of acute poliomyelitis in childhood.

In his judgment Mr. Justice Gerrard said that the operation had been completely successful and allegations of negligence against the surgeon had been rightly withdrawn. It was the anaesthetist who had administered the blood transfusion, and the judge held that he had been negligent in the circumstances of the case in not avoiding the extension of the plaintiff's arm, at any rate to the degree he permitted, for longer than necessary. He found that negligence had contributed to the very severe degree of brachial paralysis.[1] In assessing damages at £4,000 the judge took account of the plaintiff's poor state of health.

Messrs. Hempson's, acting on behalf of the Medical Defence Union, instructed counsel to hold a watching brief on behalf of the surgeon and the anaesthetist.

[1] *The Times*, April 23.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending April 11 (No. 14) and corresponding week 1952.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	19	0	9	0		22	1	10	0	3
Dysentery	325	45	81	8		548	81	55	4	1
Encephalitis, acute	5	0	0	0		4	1	0	0	1
Enteric fever: Typhoid	2	1	0	0		1	0		1	1
Paratyphoid	9	2	2(B)	0		7	0		0	2(B)
Food-poisoning	65	7		0		185	12		5	
Infective enteritis or diarrhoea under 2 years				23	22				8	67
Measles*	23,388	1032	280	209	255	6,836	231	633	227	421
Meningococcal infection	60	3	17	2	4	60	6	19	4	
Ophthalmia neonatorum	40	1	11	0		38	2	8	0	
Pneumonia†	925	51	302	15	6	711	40	304	10	
Poliomyelitis, acute: Paralytic	28	6	0	0	2	15	2	1	1	1
Non-paralytic	10	0				4	0			
Puerperal fever§	265	32	16	1		221	36	8	1	
Scarlet fever	1,266	69	171	36	52	1,361	93	183	17	57
Tuberculosis: Respiratory			155	29				150	38	
Non-respiratory			31	4				23	16	
Whooping-cough	2,618	178	288	22	95	3,004	134	266	95	45

DEATHS in Great Towns	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0		0	0	0		0	1
Dysentery	0	0				0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	1	0	0			0	0		0	
Infective enteritis or diarrhoea under 2 years	6	2	3	3	0	2	0	7	0	2
Influenza	44	5	2	2	2	33	5	6	1	0
Measles		0	1		0		0		0	0
Meningococcal infection		0	2				0			
Pneumonia	260	38	28	16	8	245	33		5	3
Poliomyelitis, acute	3	1			0	2	0			0
Scarlet fever		0	0		0		0		0	0
Tuberculosis: Respiratory	100	17	26	2	7	143	20	20	5	7
Non-respiratory		3	4	1	2		1	5	1	1
Whooping-cough	8	1	0	0	0	2	1		0	0
Deaths 0–1 year	270	25	30	15	12	249	36	44	6	15
Deaths (excluding stillbirths)	5,654	784	681	136	176	6,035	923	638	116	153
LIVE BIRTHS	8,298	1227	1050	233	410	8,204	1256	995	258	446
STILLBIRTHS	219	33	24			184	26	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Smallpox in the North Country

Up to noon, April 27, there had been 26 confirmed cases of smallpox, including 6 deaths. Since last week's report there has been one new case—in Bury C.B. This patient was a woman aged 69, vaccinated in infancy.

Infectious Diseases

In England and Wales during the week ending April 11 the number of notifications of measles increased by 2,222, from 21,166 to 23,388, and whooping-cough increased by 110, from 2,508 to 2,618, while scarlet fever decreased by 137, from 1,403 to 1,266, and dysentery by 98, from 423 to 325.

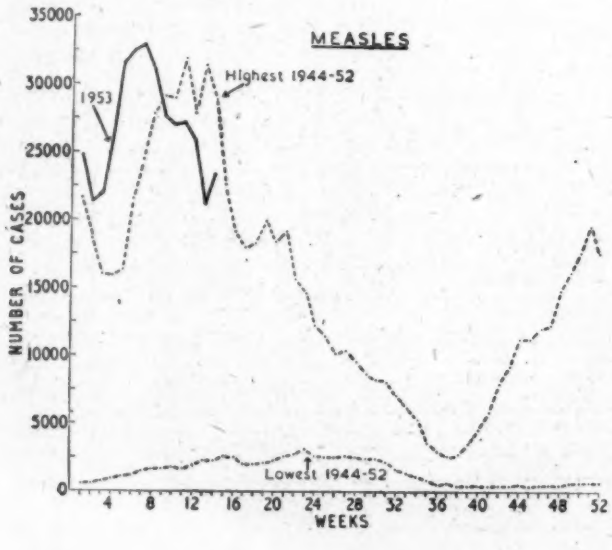
With only a few exceptions a rise in the incidence of measles was reported in every county. The largest increases were Yorkshire West Riding 515, from 1,381 to 1,896; Durham 159, from 549 to 708; the combined five south-western counties 455, from 2,089 to 2,544. The only outstanding exception to the general rise was a fall of 329 in Surrey, from 1,444 to 1,115. The largest rise in the number of notifications of whooping-cough was 44 in Durham, from 88 to 132, and the largest fall was 43 in Warwickshire, from 182 to 139. A fall of 27 in London, from 96 to 69, was the largest fluctuation in the local trends of scarlet fever. 19 cases of diphtheria were notified, 8 more than in the preceding week. The chief feature of the returns of diphtheria was a rise from 0 to 4 in Cheshire.

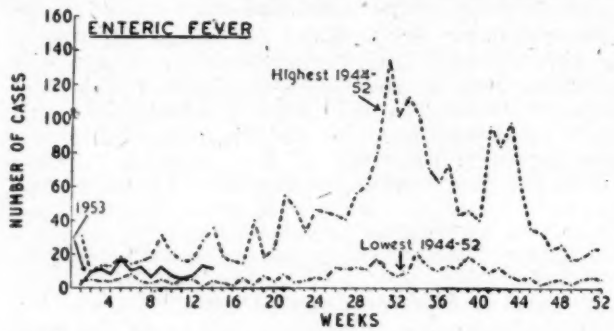
38 cases of acute poliomyelitis were notified. These were 3 fewer for paralytic and 3 more for non-paralytic cases than in the preceding week. The largest returns were London 6, Middlesex 4, Essex 4, Warwickshire 4 (Birmingham C.B. 4), and Kent 3.

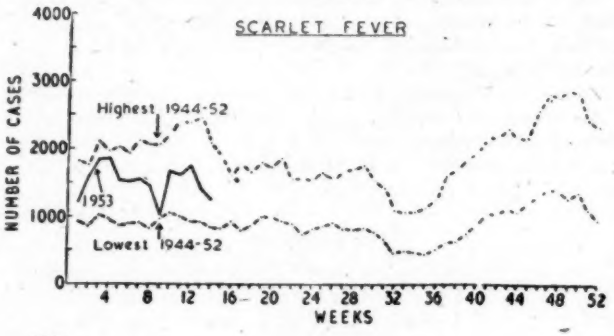
The chief centres of dysentery were Lancashire 82 (Liverpool C.B. 34, Manchester C.B. 19), London 45 (scattered through 16 boroughs), Leicestershire 41 (Leicester C.B. 41), Yorkshire West Riding 21, and Middlesex 20.

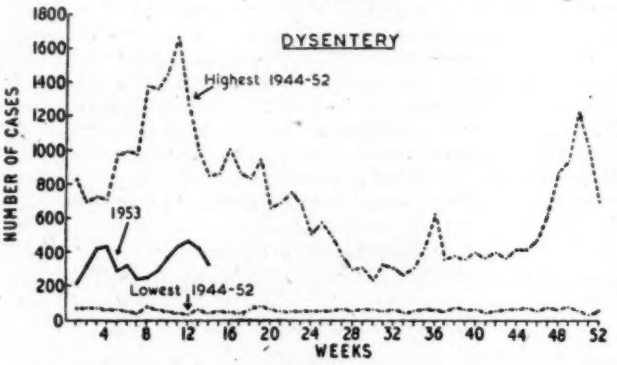
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - -, the figures for 1953 thus ————. Except for the curves showing notifications in 1953, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









England and Wales in 1951

With welcome promptitude the Registrar-General for England and Wales has produced the medical tables of his *Statistical Review* for the year 1951 only four months after the corresponding volume for 1950. The following figures extracted from it compare death rates per million in England and Wales with those in Scotland for 1951.

Cause of Death	England and Wales	Scotland
Tuberculosis of respiratory system ..	273	379
Tuberculosis, other forms	41	55
Malignant neoplasms, including neoplasms of lymphatic and haematopoietic tissues	1,951	2,065
Diabetes mellitus	84	118
Vascular lesions affecting the central nervous system	1,549	1,940
Heart diseases	3,638	4,410
Hypertensive disease	474	314

England and Wales in First Quarter

In the first quarter this year the stillbirth rate fell to a new low level for any March quarter in England and Wales, and the infant mortality rate was the second lowest. There were 3,957 stillbirths, giving a rate of 22.5 per thousand total births, as compared with 23.3 in the corresponding quarter in 1952 and 38.3 in 1938. Deaths of children under 1 year of age numbered 5,645, or 33.8 per thousand live births. This was only slightly higher than the rate of 33.4 for 1952 March quarter. The corresponding figure for 1938 was 69.3.

Deaths numbered 171,268, giving a rate of 15.8 per thousand population, as compared with 13.4 in 1952 and 19.1 in 1951 (when there was also an influenza epidemic).

Live births numbered 171,705—almost the same number as deaths—giving a rate of 15.8 per thousand population, as compared with 15.9 for 1952 and 16.3 for 1951. All figures given above relate to first quarters.—*Registrar-General's Weekly Return for England and Wales,* No. 15.

Week Ending April 18

The notifications of infectious diseases in England and Wales during the week included scarlet fever 994, whooping-cough 2,847, diphtheria 18, measles 18,861, acute poliomyelitis 34, dysentery 282, paratyphoid fever 7, and typhoid fever 2.

Medical News

Southampton Medical Society's Centenary.—The Southampton Medical Society held its centenary celebrations at the University of Southampton on Saturday, April 18. The Vice-Chancellor of the University, Mr. D. G. James, welcomed 200 members and their guests at an afternoon meeting at which Sir Russell Brain, P.R.C.P., delivered an oration on "Evolution in Medicine." The chair was taken by the president of the Society, Dr. R. S. Swindell, who was accompanied on the platform by the Mayor and Mayoress of Southampton, the Sheriff, the two Members of Parliament for Southampton, and the president of the Medical Society of London, Dr. Cuthbert Dukes. In the evening there was a dinner attended by 140 members. Amongst the guests were the Mayor, who proposed the toast of the Southampton Medical Society, the Bishop of Southampton, the Vice-Chancellor of the University, and others who had taken part in the afternoon's proceedings.

Rockefeller Foundation Grants.—In the Rockefeller Foundation's most recent quarterly report is the announcement of two substantial grants to medicine in Britain. The first is a grant of over £20,000 to the London School of Hygiene and Tropical Medicine for a three-year study in public health. This work, which is being carried out in Hertfordshire under the direction of Dr. J. H. F. Brotherston, lecturer in public health at the school, is concerned particularly with the care of the elderly sick and the use that families make of the Health Service. The second is a grant of £7,000 and $5,400 to the Welsh Regional Hospital Board for the support of the Neuropsychiatric Research Centre at Whitchurch Hospital, Cardiff. Here, under the direction of Dr. Derek Richter, work is in progress on brain metabolism, the effects of anaesthetics on the brain, hallucinations, and suggestibility. Notable grants made by the Rockefeller Foundation towards medical projects outside Britain include $500,000 for the development of the medical division of the American University of Beirut in the Lebanon, and a grant of $121,000 to the Indian Council of Medical Research for postgraduate medical fellowships.

Cerebral Palsy Centre in Belfast.—Lady Wakehurst, wife of the Governor of Northern Ireland, recently opened Malcolm Sinclair House, the cerebral palsy treatment centre of the Northern Ireland Council for Orthopaedic Development. As a result of a survey financed by the council and carried out by the Department of Social and Preventive Medicine at Queen's University it has been estimated that there are 500 spastic children in the province. The centre is intended to provide treatment for those of them likely to be able to benefit from it. After the opening ceremony Dr. C. D. S. Agassiz, physician-superintendent, Queen Mary's Hospital for Children, Carshalton, gave an address on cerebral palsy. Among those present at the opening were the Minister of Health and Local Government and the Minister of Education.

Royal National Institute for the Blind.—The Queen has commanded that the National Institute for the Blind shall in future be known as the Royal National Institute for the Blind.

Crash Helmets for Motor-cyclists.—At long last the idea of protective headgear for motor-cyclists, so ably advocated by the late Sir Hugh Cairns, is catching on with the public. Both official sources and the trade testify to this. The British Standards Institution is now preparing a standard specification for the helmets ("protective hats" in official parlance). Helmets must be light and capable of withstanding both impact and compression tests. The outer shell must be weather-proof and without dangerous projections: peaks, if worn, should be flexible. Between the harness fixing the helmet to the head and the outer shell a space with padding is recommended.

Pharmaceutical Industry and the Metric System.—Twelve months ago the annual general meeting of the Association of the British Pharmaceutical Industry adopted a resolution that bulk supplies of solid drugs, liquid galenicals, and pharmaceutical chemicals should be sold to pharmacists by metric weight and measure instead of by Imperial measure as at present. Most of the large pharmaceutical firms have agreed to this proposal. The target date for the change is July 1, but the process of altering packs and containers is bound to take some time.

Boiler-scaling and Pneumoconiosis.—By Regulations which came into force on April 22 the Minister of National Insurance has added the occupation of boiler-scaling to those covered for pneumoconiosis under the National Insurance (Industrial Injuries) Act. This will allow boiler-scalers with pneumoconiosis to obtain benefit under the Act.

Nepal and W.H.O.—At the sixth World Health Assembly, which opens in Geneva on May 5, a request from Nepal to join W.H.O. will be considered. At present there are 79 Member States and 3 Associate Members (Morocco, Southern Rhodesia, and Tunisia).

Foreign Members of the Royal Society.—Among the four distinguished scientists elected Foreign Members of the Royal Society last month were Professor M. J. C. R. Courrier, deputy director of the Collège de France, Paris, who is noted for his work on endocrinology, and Professor H. J. Muller, of Indiana, U.S.A. Professor Muller's classical experiments on the chromosomes of the fruit fly *Drosophila* are familiar to most students of biology and medicine.

Sir Robert Robinson, F.R.S., Waynflete Professor of Chemistry at Oxford, has been awarded the Priestley Medal of the American Chemical Society. This is the society's most important annual award. In the medical field Sir Robert is particularly noted for his work in connexion with the synthesis of penicillin and, more recently, of steroid hormones.

Dr. John Gillies, reader in anaesthetics at Edinburgh, has been awarded the Henry Hill Hickman medal for outstanding work in anaesthesia. The presentation is being made in London by Dr. F. M. R. Walshe, F.R.S., on May 1 at the annual general meeting of the Section of Anaesthetics of the Royal Society of Medicine.

Dr. C. B. Allsopp, D.Sc., reader in physics at Guy's Hospital Medical School, has been appointed to the London University Chair of Physics Applied to Medicine, tenable at the medical school.

Professor R. M. Walker, professor of surgery at Bristol University, has been made an honorary Fellow of University College, London.

COMING EVENTS

Territorial Medical Officers' Dinner.—The annual dinner of the Territorial Army Medical Officers' Association will be held on May 8. Further particulars concerning the dinner can be obtained from the honorary secretary, 19, Queen Anne Street, London, W.1.

Grenfell Volunteers' Reunion.—The annual reunion of Grenfell Volunteers will take place at the Overseas League, Park Place, St. James's Street, London, S.W.1, on May 6, from 3 p.m. to 5.30 p.m. The speaker will be Dr. W. A. Paddon, who is in charge of the hospital station at North-west River, and the chair will be taken by the Reverend Henry Gordon.

Society for Endocrinology.—A symposium entitled "The Determination of Adrenal Cortical Steroids and Their Metabolites" will be held by the Society of Endocrinology at the Medical Society of London, Chandos Street, London, W.1, on May 21 at 9.30 a.m. Non-members wishing to attend are asked to communicate with Professor N. F. Maclagan, Westminster Medical School, London, S.W.1.

National Marriage Guidance Council.—The seventh annual conference of the National Marriage Guidance Council is to be held at Llandudno from May 14 to 17. The theme of the conference will be "Marital Conciliation," and those wishing to attend are asked to communicate with the office secretary, National Marriage Guidance Council, 78, Duke Street, Grosvenor Square, London, W.1, from whom further details may be obtained.

Laboratory Animals.—The Laboratory Animals Bureau has arranged a symposium on laboratory animals to be held at the Royal Society of Medicine, 1, Wimpole Street, London, W.1, on May 14 at 2.30 p.m. The chairman will be Dr. H. J. Parish, and other speakers include Mr. A. N. Worden, Mr. A. E. Mundy, Mr. J. Scarnell, and Dr. J. S. Paterson. The symposium will be followed by an open discussion.

NEW ISSUES

British Journal of Ophthalmology.—The next issue of this journal (Vol. 37, No. 5) will be available in a week's time. The contents include:

NOTES ON OPHTHALMOLOGICAL PRACTICE IN LUND. Sven Larsson.
CAUSES AND TREATMENT OF CONGENITAL ECCENTRIC NYSTAGMUS. J. Ringland Anderson.
ARTERIOLAR INVOLVEMENT IN DIABETIC RETINOPATHY. Norman Ashton.
VASCULAR CHANGES THAT OCCUR DURING THE PHASIC VARIATIONS OF TENSION IN CHRONIC GLAUCOMA. J. H. Dobree.
CORNEAL THICKNESS IN INTERSTITIAL KERATITIS. Charles Cook and Maurice Langham
EXPERIENCES WITH THE LINDNER-GUIST OPERATION. A. Lister.
CORRESPONDENCE BETWEEN VISUAL ACUITY, REFRACTIVE ERROR, AND THE SPEED OF VISUAL PERCEPTION. T. H. Eames.
UNUSUAL APPEARANCE IN A CASE OF EALES'S DISEASE. A. G. Cross and D. P. Choyce.
INFRA-RED IMAGE CONVERTER IN ROD SCOTOMETRY. M. F. P. Marshall.

Issued monthly; annual subscription £4 4s., single copy 8s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, May 4

CAMBRIDGE UNIVERSITY.—At Department of Pathology, 4.30 p.m., Dr. P. Lépine (Institut Pasteur): Electron Microscope Studies in the Virus Field. with Special Reference to the Study of Intracellular Development of Viruses.
●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. H. Wirz (Basle): Osmotic Work of Mammalian Kidney.
UNIVERSITY COLLEGE.—At Physiology Theatre, 4.45 p.m., Sir Rudolph Peters, F.R.S.: Inhibitors and Intracellular Chemical Dissection.

Tuesday, May 5

CAMBRIDGE UNIVERSITY.—At Department of Pathology, 4.30 p.m., Dr. P. Lépine (Institut Pasteur): Present Position of the Poliomyelitis Problem: Research and Epidemiology.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. E. J. Moynahan: Urticaria.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Humphry Davy Rolleston Lecture by Professor R. A. McCance, F.R.S.: Overnutrition and Undernutrition.
ROYAL EYE HOSPITAL.—5 p.m., Mr. T. M. Tyrrell: Cataract Surgery and its Complications.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Dr. D. Hunter: Prevention of Occupational Disease.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School.—5 p.m., Almroth Wright Lecture by Dr. Leonard Colebrook, F.R.S.: Almroth Wright—Pioneer in Immunology.

Wednesday, May 6

●BRITISH MEDICAL ASSOCIATION.—6.30 p.m., Sir Charles Hastings Lecture by Professor F. A. E. Crew, F.R.S.: Medicine and Social Policy.
INSTITUTE OF DENTAL SURGERY.—5 p.m., Dr. F. W. Clement (Toledo, U.S.A.): General Anaesthesia in Dental Surgery.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Histology of Normal Skin.
LONDON UNIVERSITY.—At School of Pharmacy, 5.30 p.m., Dr. W. O. Jones, F.R.S.: Formation of Alkaloids in Plants.
OXFORD UNIVERSITY.—At University Museum, 5 p.m., Litchfield Lecture by Professor W. T. Astbury, F.R.S.: Some Leading Questions in the Fine Structure of Biological Fibres.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. R. J. Ludford: Tissue Cultures—Pathological Aberrations of Cellular Structure and Functioning.

Thursday, May 7

FACULTY OF HOMOEOPATHY.—5 p.m., Dr. D. M. Gibson: Observations on Homoeopathy in Relation to Psychoneurosis.
●HAMPSTEAD GENERAL HOSPITAL.—3 p.m., Dr. D. Hector-Jones: Radiology of the Large Gut; 4.15 p.m., Mr. Harland Rees: Urinary Calculi.
LONDON UNIVERSITY.—At School of Pharmacy, 5.30 p.m., Dr. W. O. James, F.R.S.: Formation of Alkaloids in Plants.
●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. H. S. Banks: Acute Meningitis.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Humphry Davy Rolleston Lecture by Professor R. A. McCance, F.R.S.: Overnutrition and Undernutrition.
ROYAL EYE HOSPITAL.—5.30 p.m., Miss M. Savory: Influence of Cortisone on Inflammatory Eye Conditions.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Dr. J. L. Nickerson: Current Research in Ballistocardiography.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. M. A. Partridge: postgraduate demonstration in psychiatry.

Friday, May 8

INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. F. R. Bettley: Atopy.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Mr. T. Holmes Sellors: Treatment of Pleural Infection.
●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. Russell Fraser: Use of Radio-iodine in Thyroid Diagnosis.
ROYAL EYE HOSPITAL.—5.30 p.m., Miss J. M. Dollar: Surgery of the Orbit.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Obstetric and Gynaecological Conference. Dr. Hugh McLaren: Early Diagnosis of Carcinoma of the Cervix.

Saturday, May 9

WEST MIDLANDS PHYSICIANS ASSOCIATION.—At Gulson Hospital, Coventry 11 a.m., general meeting

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Aitken.—On March 2, 1953, at Queen Charlotte's Hospital, London, W., to Jean, wife of Dr. C. A. M. Aitken, a son—Timothy John McClelland.
Bailey.—On April 7, 1953, to Jeanne, wife of David Bailey, F.R.C.S., twins—Timothy and Patricia.
Benstead.—On March 30, 1953, at the Christiana Hartley Maternity Hospital, Southport, to Drs. Nancy and John Benstead, a son—Richard John Rand.
Cameron.—On April 3, 1953, at Maryfield Hospital, Dundee, to Frances, wife of H. MacDonald Cameron, M.B., B.Ch., D.Path., a son.
Charlton.—On April 16, 1953, to Maureen (formerly Rodgers), M.S.R., wife of John C. Charlton, M.B., B.Ch., of Lurgan, Station Road, Mickleover, Derby, a son.
Comper.—On April 18, 1953, at Farnborough Hospital, Kent, to Pamela (formerly Mayes), wife of Dr. John Comper, a son.
Drewitt.—On March 18, 1953, at Ivy Lodge, Lockwood Street, Driffield, Yorks, to Kathleen Rose (formerly Blair), S.R.N., wife of Dr. A. H. Drewitt, a daughter—Suzanne Elizabeth Blair.
Evans.—On April 10, 1953, at the Hammersmith Hospital, London, W., to Marjorie, wife of Lynn A. J. Evans, F.R.C.S., a son.
Forbes.—On April 15, 1953, to Pamela, wife of John Forbes, M.D., of Pen-y-wern, near Mold, Flintshire, a son.
Foxell.—On April 13, 1953, at Suffolk House Nursing Home, Stanmore, Middlesex, to Maureen, wife of Dr. Alan Foxell, a son.
Manson.—On April 4, 1953, at Moffat Hospital, Kanye, Bechuanaland Protectorate, to Jocelyn, M.S.R., C.T., wife of John M. S. Manson, M.D., D.T.M.&H., D.Obst.R.C.O.G., a daughter.
Pickford.—On April 14, 1953, at Wisbech, Cambridgeshire, to Whinifred, wife of Dr. Steven Pickford, a son.
Powell.—On April 1, 1953, at Amman Valley Hospital, Glanamman, Carmarthenshire, to Muriel (formerly Davies), wife of Dr. F. I. Powell, "Brynteg," Garnant, Carmarthenshire, a son—David Huw.
Pratt.—On April 12, 1953, at the Duke of York Nursing Home, Bradford, Yorks, to Dorothy (formerly Boothroyd), S.R.N., wife of Dr. Peter Pratt, a brother for Christopher.
Scriven.—On April 20, 1953, at Wrecclesham Grange Nursing Home, Farnham, Surrey, to Dr. Jeanne (formerly Edwards), wife of Dr. W. H. Scriven, M.B.E., a son.
Watkinson.—On April 5, 1953, at St. James's Hospital, Leeds, to Marie, wife of Dr. Geoffrey Watkinson, a brother for Anne.
Welch.—On April 11, 1953, at Elvet House, Dean Road, South Shields, to Dr. and Mrs. H. D. Welch, a daughter.

MARRIAGES

Newborne—Skelton.—On April 18, 1953, at St. Giles Church, Oxford, Laurence Perceval Anthony Newborne, M.D., to Mary Skelton, M.C.S.P.
Tannert—Whatley.—On April 11, 1953, in London, John Tannert to Elizabeth Whatley, M.B., B.S.

DEATHS

Corfield.—On March 20, 1953, at the Middlesex Hospital, London, W., Walter Francis Corfield, M.D., D.P.H., formerly of Colchester, Essex, aged 73.
Croft.—On April 21, 1953, at Lawn Bank, Tarleton, near Preston, Lancs, Lawrence Croft, M.B., B.S., aged 71.
Davies.—On March 21, 1953, at "Conquerors," Stunts Green, Hurstmonceaux, Sussex, Frederick Spencer Davies, M.R.C.S., L.R.C.P., late of Buckhurst Hill and Harlow Common, Essex.
McGowan.—On March 20, 1953, at his home, 18, Clare Road, Halifax, Joseph McGowan, M.B., B.Ch.
Sutton.—On March 19, 1953, Margaret Joan Sutton, L.R.C.P.&S.Ed., L.R.F.P.S., of Poynton Park, Poynton, Cheshire, aged 28.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Prophylactic Chemotherapy of Measles

Q.—*Some practitioners favour the prophylactic use of sulphonamides or penicillin in the early stages of measles. Is any evidence available to prove that such treatment cuts down the incidence of complications due to secondary bacterial invaders?*

A.—The early damage to the cells of the mucous membrane in measles is virus-induced and cannot be affected by chemotherapy. The effect of this damage, however, is to produce a "soil" which facilitates bacterial infection so that the majority of the complications are bacterial in nature. There thus seems a reasonable case for prophylactic chemotherapy. But, when considering chemoprophylaxis, two different situations must be borne in mind. In the open hospital ward the child will be exposed to the bacterial flora of many unrelated persons. The danger of acquiring a secondary bacterial infection is therefore increased, and prophylactic penicillin is worth considering. When so used, the danger of inducing a chronic ward infection with a penicillin-resistant strain must be kept in mind; if complications arise unexpectedly, the organism isolated must immediately be tested for sensitivity and appropriate steps taken.

In private practice the argument for prophylactic chemotherapy is less sound. Here the patient will be exposed solely to the family bacterial flora, and secondary infection will be less commonly encountered. Further, the danger period is short—three to five days—and during this time the child should be under daily clinical observation, so that it should be possible to bring any complication which does arise under immediate control. My own view is that such treatment should be considered only between the age of 6 months to 2 years, and even then only in the severe case of measles. It should never become a routine, but always be guided by clinical judgment.

Finally, one might perhaps emphasize that the complication of greatest importance is otitis media. For this reason the drumheads should be inspected daily during the early danger period so that penicillin may be started at the earliest sign of inflammation.

(In the earliest days of the sulphonamides their value as prophylactics was reasonably well established, but one would now hesitate to advocate their use for this purpose in view of their toxicity and the greater efficiency of penicillin.)

Seaweed Baths

Q.—*What is the therapeutic basis for the use of seaweed baths? What do they contain, in what conditions are they useful, and how are they given?*

A.—The procedure of this bath is as follows: fresh seaweed is treated with boiling water until a jelly is produced; the jelly is added to a reclining-bath of warm sea-water in which the patient immerses himself. Subsequently the patient is given an ordinary sea bath, rubbed down, and packed in hot towels. These baths are available only at a few seaside resorts; no chemist's pack containing seaweed is on the market.

Seaweed thus administered can have no specific action, as none of its constituents will be absorbed through the skin. The total effect of the procedure outlined above is similar to that of an ordinary warm reclining-bath—namely, it brings about relaxation of the patient as a whole and of the muscles and joints in particular. This effect will be temporary only.

Dangers from the Use of Relaxants in E.C.T.

Q.—*As a psychiatrist without any special anaesthetic training, is there any unwarrantable risk in my administering a relaxant, such as succinylcholine or gallamine triethiodide, with small doses of a barbiturate before E.C.T.? What precautions should I take apart from having facilities for controlled respiration? What are the dangers of laryngeal spasm and of cardiac arrest, particularly in senile patients?*

A.—If the doses of the relaxant and of the barbiturate are correct for the particular patient, the only real risk involved is that of temporary respiratory arrest. The administrator should have sufficient experience and confidence in performing rhythmic inflation of the lungs to maintain good ventilation until spontaneous breathing returns. This will usually be within a few minutes. Very occasionally the return of spontaneous breathing may be delayed for longer. Even so, adequate and correctly performed controlled respiration will tide the patient over until the effects of the relaxant have worn off. There is little danger of spasm of the glottis with these relaxants unless for some reason mucus or stomach contents come in contact with the larynx during the recovery phase. In any case, if the barbiturate dosage is small no harm will result. Cardiac arrest during E.C.T. is no more likely to occur with a relaxant than without, so long as adequate oxygenation is maintained at all times.

Phosphorus Poisoning

Q.—*It is stated that in phosphorus poisoning no oil may be given. Could you tell me the reason for this and what harm the oil might do? Also, what is the chemical reaction of potassium permanganate in such cases?*

A.—Phosphorus is insoluble in water, but readily dissolves in fat. In the absence of fat it is absorbed from the alimentary tract, but the speed with which it would be absorbed would almost certainly be increased if edible oil were given. Liquid paraffin, however, has been recommended in treatment presumably because it is not absorbed and carries away the phosphorus in it.

Potassium permanganate oxidizes phosphorus to its oxides, which in turn react with water to form phosphoric acids. Both the reagent and products of the reaction will be extremely irritating to the stomach. Repeated gastric lavage is probably the most rational therapy.

Aspermia

Q.—*A healthy man of 30 is sterile owing to complete aspermia. What is the aetiology, prognosis, and correct method of investigation and treatment?*

A.—This is a formidable question, the full answer to which is quite outside the scope of "Any Questions?" The aetiology can be either obstructive, spermatozoa being prevented by duct blockage from reaching the urethra, or due to failure of spermatogenesis. The former most commonly follows infection of the upper genital tract (e.g., gonococcal epididymo-orchitis), but may also be the result of aplasia of the vas or congenital anomalies of the epididymis. Failure of spermatogenesis may be the result of primary or secondary hypogonadism, congenital absence of the germinal epithelium,[1] trauma, or infection. Mumps after puberty, with bilateral orchitis, may result in testicular atrophy and aspermia (though this is not invariable). Hernia operations may be followed by testicular ischaemia and resultant failure of spermatogenesis. If the testicles are not in the scrotum at puberty, spermatogenesis is unlikely to occur and aspermia follows.

The prognosis clearly depends upon the aetiology. If the germinal epithelium is destroyed the condition is hopeless; if spermatogenesis has never started (secondary eunuchoidism) there is a hope of stimulating it by suitable treatment.[2,3] If spermatogenesis is taking place and the duct system is blocked, surgery offers a potential solution.

Investigation involves repeated seminal analysis to establish the existence of the condition (a single aspermic ejaculate means very little). If the testicles are small, urinary follicle-stimulating hormone assay will differentiate primary hypogonadism (with a high F.S.H. titre and hopeless prognosis) from secondary failure (with a low titre). If the testicles are normal in size, testicular biopsy will reveal the existence of spermatogenesis, thus indicating an excretory block; or else damage to the germinal epithelium. However, according to Bayle,[4] testicular biopsy causes a risk of blocking the vasa efferentia as a result of the slight haemorrhage which is inevitable; he therefore advocates open surgical exploration of the testicle with incision of the head of the epididymis. If this reveals the presence of spermatozoa, and patency of the vas deferens can be established, then vaso-epididymostomy is performed—bilaterally whenever possible. In surgically suitable cases this operation has given a 66% cure rate in Bayle's hands. Apart from surgery for obstructive aspermia, treatment appears to hold out hope only when there is secondary hypogonadism as mentioned above. Then prolonged treatment with testosterone (preferably by implantation) or with chorionic gonadotrophin seems to have led to normal fertility at least in some patients. For further information the reader may be referred to the monograph by Hotchkiss.[5]

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1 del Castillo, E. B., Trabucco, A., and de la Balze, F. A. (1947). *J. clin. Endocr.*, 7, 493.
2 Hurxthal, L. M., Bruns, H. J. and Musulin, N. (1949). *J. clin. Endocr.*, 9, 1245.
3 Swyer, G. I. M. (1951). *Proc. roy. Soc. Med.*, 44, 157.
4 Bayle, H. (1950). *Presse méd.*, 58, 276.
5 Hotchkiss, R. S. (1944). *Fertility in Men*. Lippincott.

Unnecessary Vitamin B

Q.—*Is any harm likely to follow prolonged dosage with any of the B vitamins when the diet is already adequate in this respect?*

A.—There is no direct evidence that the prolonged dosage of well-nourished people with any of the B vitamins is likely to be harmful. Theoretically, an excess of one might cause imbalance of the others, as has been claimed to occur in cases of subnutrition; and the manufacture of B vitamins, such as nicotinic acid, by intestinal organisms might be suppressed by the administration of large exogenous doses. It is unlikely, however, that these theoretical objections have practical validity.

Allergy to Condoms

Q.—*A man who has used a well-known make of condom for years has in the last few months been troubled with itching, redness, and, on one occasion, oedema of the skin of the penis for a few days after use of the sheath. The irritation is relieved by an antihistamine cream. Is the powder on the condom likely to be the irritant? Is a change of make desirable, or do most manufacturers treat sheaths with the same powder? The man is unwilling to complicate intercourse further by using any sort of "barrier cream" unless this is really necessary.*

A.—Sensitivity to rubber seems far more likely than sensitivity to the powder. This point could be settled by carrying out a patch test with rubber which has been carefully washed to remove any of the powder, and another patch test either with the powder alone or with rubber on which powder has been allowed to remain. Sensitivity to rubber is usually due to chemicals used in processing rather than to the rubber itself. For this reason sensitivity to one type or brand of rubber does not necessarily imply sensitivity to others. Manufacturers are not always very willing to reveal the exact composition of their products, and once the dermatitis has been definitely identified as due to contact sensitivity the best plan for the patient would be to try various makes in order to find one which will not bring on this trouble.

A barrier cream, in any event, is not likely to be successful, and in a case of this sort the only solution will be for the patient to avoid this particular make of rubber.

NOTES AND COMMENTS

C.S.F. Changes in Psychoses and Epilepsy.—Dr. J. H. FLEISCHHACKER (Shenley) writes: My attention has been drawn to the question and answer on C.S.F. changes in psychoses and epilepsy ("Any Questions?" January 31, p. 285), where a paper of mine was mentioned. While it is true that the problem—with the techniques used in this laboratory—has been followed up systematically only by myself and co-workers,[1 2 3 4] it may be said that an increase of globulins in the C.S.F. of schizophrenics was described first by Golant-Ratner,[6] later by Kafka and Samson[8] and Neal *et al.*[7] All authors used different techniques, and came to the same conclusions. Such findings have since been confirmed among others by Schenk[9] and von Storch *et al.*,[9] and also by German and French workers.[10] These findings, though "typical" only and "non-specific," are in my opinion of high differential-diagnostic significance, but their pathogenetic or aetiologic importance is not clear.[4] The controversy about the value of these findings is due, essentially, to the fact that there is no agreement on the "norm of C.S.F.s."[4 11] I cannot help feeling that C.S.F. from patients suffering from organic and often active diseases of the C.N.S. should not be considered as "normal."

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5 *Münch. med. Wschr.*, 1924, 71, 1128.
6 *Z. ges. Neurol. Psychiat.*, 1928, 115, 85.
7 *Acta psychiat. neurol. scand.*, 1933, 8, 609.
8 Ibid., 1940, 15, 151.
9 *Arch. Neurol. Psychiat. (Chicago)*, 1950, 64, 668.
10 Personal communications.
11 *British Medical Journal*, 1950, 2, 218.

Toxaemia in Pregnancy.—Dr. JOHN SOPHIAN (Salisbury, Southern Rhodesia) writes: In your issue of February 21 (p. 466) you furnish a reply to a correspondent inquiring under "Any Questions?" about the present view of the aetiology and pathology of toxaemia of pregnancy. In this you state that the present tendency is to regard its aetiological basis as uterine and placental ischaemia. Reynolds[1] has shown the interdependence of uterine blood flow on tension of the uterine wall in the rabbit. He has also demonstrated[2] the fact that the primiparous uterus develops marked heightening of tension from the 20th week onwards—a period during which toxaemia of pregnancy has its greatest incidence. Such researches indicate with certainty that the aetiological thesis must include increased tension of the uterine wall in its explanation when it is appreciated that it has been shown in rabbits by Franklin and Sophian[3] that diversion of the renal blood flow from cortex to medulla is provoked by increasing the uterine tension. Especially is confirmation to be found in the renal manifestation of the toxaemic state. In the great majority of diseases of the kidney oedema and albuminuria have never been denied a renal origin. Ischaemia of the kidney has been invoked by Goldblatt[4] and Shorr and Zweifach[5] as responsible for the production of renal pressor substances. The triad of symptoms can have their explanation in ischaemic renal changes which the utero-renal reflex can provoke. In its turn the reflex is dependent on heightened tension of the uterine wall, which Reynolds has found to be present in the primiparous uterus in that period usually contemporaneous with toxaemic manifestations. Reduced blood flow in uterus and placenta is material in considering foetal survival alone. But the toxaemic state imperils the maternal organism as well, and your reply has failed to include its consideration.

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1 *Physiology of the Uterus*, 1949, 2nd ed., p. 337. Hoeber, New York.
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4 *Amer. J. Med.*, 1948, 4, 100.
5 *Amer. Heart Ass. Proc.*, 1949, 22nd sci. session, June.

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